NCT number: NCT03284957

AMENDED CLINICAL TRIAL PROTOCOL 10

COMPOUND: amcenestrant (SAR439859)

A Phase 1/2 study for the safety, efficacy, pharmacokinetic and pharmacodynamics evaluation of amcenestrant (SAR439859), administered orally as monotherapy, then in combination with other anti-cancer therapies in postmenopausal women with estrogen receptor-positive advanced breast cancer

STUDY NUMBER: TED14856

VERSION DATE/STATUS: 08 December 2021 / Approved

Study name: AMEERA-1

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NAMES AND ADDRESSES OF

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 10	All	08 December 2021, version 1 (electronic 11.0)
Amended Clinical Trial Protocol 09	All	23 March 2021, version 1 (electronic 10.0)
Amended Clinical Trial Protocol 08	All	30 October 2020, version 1 (electronic 9.0)
Amended Clinical Trial Protocol 07	All	03 April 2020, version 1 (electronic 8.0)
Amended Clinical Trial Protocol 06	All	02 October 2019, version 1 (electronic 7.0)
Amended Clinical Trial Protocol 05	All	02 August 2019, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 04	All	29 January 2019, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 03	All	27 July 2018, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02	All	23 July 2018, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	15 June 2017, version 1 (electronic 1.0)
Original Clinical Trial Protocol		30 March 2017, version 1 (electronic 5.0)

AMENDED PROTOCOL 10 (Date 08 December, 2021)

This Amended Protocol 10 (Amendment 10) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The objective of the amendment is to

1. Change the recommendation for amcenestrant 200 mg to only be taken with food in the combination cohorts
2. Clarification of the inclusion criteria I 06 language
3. Modification of exclusion criteria E13 to allow fulvestrant as a prior therapy in dose escalation study parts
4. Removal of the exclusion criteria E20: treatment with drugs that are P-gp sensitive substrate, BCRP sensitive substrate, and UGT inhibitors are no more prohibited following recent clinical data.
5. Modification of the exclusion criteria E21: extension of the exclusion criteria E21b to Arm#5 patients under full PK sampling as they will also have 4βOH cholesterol assessment.

6. Addition of the exclusion criteria E40 to prohibit use of medicines which are OATP1B1/1B3 substrate sensitive
7. Modification of 8.6 Concomitant Therapy (1/ PgP and BCRP sensitive substrate, UGT inhibitors, anti-acids, H2 antagonists, Proton Pump Inhibitors are no more prohibited. 2/ sensitive substrates of OATP1B1/1B3 are prohibited)
8. Adding the language concerning the avoidance of concomitant use of QT prolonging drugs for patients in Arm#3 (Parts F and G) per Canadian Health Authorities request
9. Modification of the Arm#2 cut-off date (COD). The PFS in Arm#2 was expected to be mature at LPI+12 months based on the available data from the literature and patients' population. However, observed Arm#2 PFS data were not mature at LPI+12 months, and the COD for this Arm has been changed to LPI+20 months. That way, mature PFS data will be collected for ongoing Arm#2 patients.
10. Addition of the Benefit/Risk Assessment sub-section to reflect the latest benefits and risks for amcenestrant as mentioned in other AMEERA protocols, and all anti-cancer agents used in the study combinations, as well as benefit-risk in the context of the COVID-19 pandemic
11. Correction of any typo and inconsistencies

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Global	Food conditions for all amcenestrant combinations was updated	Updated to reflect new PK food study findings and recommendation for amcenestrant administration in combination cohorts
Global	"moderate fat breakfast" was replaced with "standard meal"	Updated to reflect FDA's guideline definitions
Title page	"Amcenestrant" was added to title page and the sponsor company address was updated	The compound official name was added and the correct company address
Clinical trial summary and Section 5.1 Primary Objectives	Objectives were reorganized	Objectives were reorganized for clarity
Clinical trial summary and Section 5.2 Secondary Objectives	Participants from Arm#5 Parts J and K with full PK sampling were added	Objectives were updated for the assesment of potential induction/inhibition effects of amcenestrant on CYP450
Clinical trial summary and Section 5.3 Exploratory Objectives	Arm#3 was added to sections on confirming the ER degradation with re-biopsy of the tumor.	Error correction to reflect biopsies for new combinations.
Clinical trial summary and Section 6.10 Study Committees	Revised the description of the Study Committee and their roles in the study	To improve the clarity of the contributors and their functions
Clinical trial summary and Section 7.2 Inclusion Criteria	I 06 was revised	To improve recruitment

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary and Section 7.3.2 Exclusion criteria related to the disease	E 13, 20, 21, 22, 24, 25, and 39 were modified. E 40 was newly added	Exclusion criteria were modified to allow fulvestrant as a prior therapy in dose escalation study parts, to reflect new DDI risk information, to add back information mistakenly removed in amended protocol 09, and to provide clarity of language
Clinical trial summary and Section 8.1.1.3 Alpelisib	Removed “150 mg”	Updated to reflect actual drug supply
Clinical trial summary (secondary endpoint)	Secondary endpoint was modified to include “Part J, Part K), or Cycle 2 Day 28 versus Day 1 Cycle 1 (Part J, Part K)”	To update and improve the clarity of the secondary objective/endpoint
Clinical trial summary (exploratory endpoint)	Updated the ER degradation exploratory endpoint	To improve clarity of the language and to reflect the updated study arms and parts involved
Clinical trial summary and Section 13.9.5.1 Analyses of pharmacokinetic variables	Added “4β-hydroxy/total cholesterol concentration ratio (Cycle2/Cycle1) will be estimated with 90% CI.”	To update statistical considerations involved for Arm #5 Part J
Clinical trial summary and Section 6.8.1 Duration of the study participation for each patient	Modification of COD. Also, “After the final COD” was replaced with “After each study Arm COD”	COD was modified to allow mature PFS data collection for ongoing Arm#2 participants. Texts were modified for improved clarity
Section 1.2 Graphical study design – study scheduling	Graphical study design figure was replaced	Correction to show the missing information prior to the screening period and to update the product code with the product name
Section 1.3 Study Flowchart	Removed “for F and G only” for Molecular profiling in cfDNA (NGS, plasma) on D28 (±2). Added footnote jj. Footnotes b, g, i, l, x, y, z, and gg were modified	Footnotes and table were updated to reflect the food effects of amcenestrant and to provide further clarity of the study
Section 1.4.3.1 Part F and G	Removed: “The Sponsor will evaluate if the patient has a mutation of interest by cfDNA analysis during the screening period.”	Correction, since this sentence refers to cfDNA and not to biopsy
Section 1.4.3.1.1 Full PK sampling (Parts F and G)	An “X” was placed under the 24 h column	Updated to reflect amcenestrant administration start at Day 3 T24h
Section 1.4.4.1 Parts H and I	Footer a was modified	Updated to reflect food effects for amcenestrant combinations
Section 1.4.5.1.1 Parts J and K, full PK sampling	Footer a was modified. Also, P02 was moved to column for day 28	Footer updated to reflect food effects for amcenestrant combinations and table modified to allow PK collection on C2D28
Section 4.1.1 Benefit/Risk Assessment	Benefit/risk assessment section was added. Subsequent tables were renumbered.	This section was added to reflect the latest benefits and risks of amcenestrant and the anti-cancer agents used in the study combinations, as well as the risks in the context of the COVID-19, and to align with other AMEERA studies which also have this section in their protocols
Section 4.2 Description of Amcenestrant	Updated description of amcenestrant	Updated to reflect the MOA agreed by the study team and for clarity of language

Section # and Name	Description of Change	Brief Rationale
Section 4.3.1 Preclinical data	Modified text in metabolism and preclinical pharmacokinetics	Updated to reflect in vitro data
Section 4.4.3.2 Part G (Dose Expansion, Combination with alpelisib)	Replaced v4 with v4.03	Updated to reflect correct NCI-CTCAE version
Section 6.6 Expansion Cohorts to Confirm the Maximum Tolerated Dose	Added “In Part I, approximately 12 patients are planned to be treated. In Part K, approximately 20 patients are planned to be treated.”	Updated to include information on patients planned to be treated with everolimus and abemaciclib combinations
Section 8.5.1 Treatment accountability and compliance	Added everolimus and abemaciclib after “amcenestrant and/or palbociclib/alpelisib” as potential combinations with amcenestrant, modified arms for amcenestrant, and the text regarding patient diary logs was modified	Updated to reflect amcenestrant combinations involved in the study and to improve clarity
Section 8.6 Concomitant Treatment	Content regarding concomitant medications in treatment arms were updated. Also, added “Arm#5 Part J and K (for patients with full PK sampling”	Content was updated to reflect the amcenestrant drug-drug interaction risk and per Canadian Health Authority request. Text was also updated to provide clarity.
Section 9.2.2 Pharmacokinetic sample handling procedure	In table 33, “The remaining liquid blood will be diluted (v/v) with water” was replaced with “The remaining liquid blood samples are guard samples. They must remain stored in the BA lab until the end of the analysis of the DBS samples.”	Updated to reflect the most up to date recommendations of the handling procedures
Section 9.2.3 Bioanalytical method	In tables 36 and 37, changed names of sites of bioanalysis from Covance to LabCorp for everolimus and for all other sites, names were replaced with Pyxant	Updated to reflect the correct names of sites for this study
Section 9.3.1 Optional drug metabolizing enzymes and transporters DNA sample	Replaced patients who signed the optional pharmacogenetic ICF with “patients who select to do the optional pharmacogentic assessment in the Main ICF”	Correction, to clarify that there is no separate pharmacogentic ICF a patient will sign
Section 9.6 Future Use of Samples	Rephrased the sentence regarding leftovers from used samples and their potential uses of research	To improve clarity of language

Section # and Name	Description of Change	Brief Rationale
Section 13.9.2 Extent of investigational medicinal product exposure	Removed: "in the expansion parts of the study (dose expansion Arms #1, #2, #3, #4, and #5 [Parts B, D, G, I and K])", added in Arm#3, and removed specifications of Arm#5 parts involved	Correction to improve clarity, as this section is not just limited to expansion parts. Also, updates were made to reflect the arms involved in cycle delays
Section 13.9.4.2 Analyses of adverse events	Added version number (v4.03) to NCI-CTCAE version	Updated to reflect correct NCI-CTCAE version
Section 13.10 Interim Analysis	Removed a paragraph regarding Arm #1 Part B, mentioning the planning of an interim analysis when 29 patients are treated	This paragraph was removed in order to fix an error from the previous amended protocol
Section 14.2 Informed Consent	Modified the informed consent section	Updated to improve clarity on the different ICFs involved and to clarify the information on pharmacogenetic ICF, as there is no separate pharmacogenetic ICF
In addition, other minor editorial changes (eg, grammatical, stylistic, and minor typographical error corrections) were implemented throughout the protocol.		

CLINICAL TRIAL SUMMARY

COMPOUND: SAR439859 STUDY No: TED14856 AMEERA-1

TITLE	A Phase 1/2 study for the safety, efficacy, pharmacokinetic and pharmacodynamics evaluation of amcenestrant, administered orally as monotherapy, then in combination with other anti-cancer therapies in postmenopausal women with estrogen receptor-positive advanced breast cancer
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	1/2
STUDY OBJECTIVES	**Primary objective** **DOSE ESCALATION:** **Monotherapy Arm #1 – PART A (amcenestrant monotherapy); Combination Arm #2 – PART C (amcenestrant in combination with palbociclib); Combination Arm#4 - PART H (combination of amcenestrant with everolimus); Combination Arm #5 - PART J (combination of amcenestrant with abemaciclib)** • To assess the incidence rate of dose-limiting toxicity (DLT) and to determine the maximum tolerated dose (MTD) as well as the recommended dose (RD) of amcenestrant administered as monotherapy (Part A), then in combination with palbociclib (Part C), in postmenopausal women with estrogen receptor (ER) positive and human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. • To assess the incidence rate of dose-limiting toxicity (DLT) and determine the recommended dose (RD) of everolimus (Part H) or abemaciclib (Part J) administered in combination with the selected amcenestrant dose for the combination therapy **SAFETY RUN-IN Phase:** **Combination Arm #3 – PART F (combination of amcenestrant with alpelisib)** • To confirm the recommended dose (RD) of amcenestrant in combination with alpelisib in postmenopausal women with ER positive, HER2 negative and PIK3CA-mutated advanced breast cancer. **DOSE EXPANSION:** **Monotherapy Arm #1 – PART B (amcenestrant monotherapy)** • To assess antitumor activity using objective response rate (ORR) according to response evaluation criteria in solid tumors (RECIST) v1.1 determined by an Independent Central Review (ICR) at the amcenestrant RD administered as monotherapy (Part B) in postmenopausal women with ER-positive and HER2-negative advanced breast cancer. **Combination Arm #2 – PART D (combination of amcenestrant with palbociclib); Combination Arm #3 – PART G (combination of amcenestrant with alpelisib); Combination Arm #4 – PART I (combination of amcenestrant with everolimus); Combination Arm #5 – PART K (combination of amcenestrant with abemaciclib)** • To characterize the overall safety profile of amcenestrant administered in combination with palbociclib (Part D), in combination with alpelisib (Part G), in combination with everolimus (Part I), and in combination with abemaciclib (Part K)

	Secondary objectives • To characterize the overall safety profile of amcenestrant administered as monotherapy (Arm #1 Parts A and B), in combination with palbociclib (Arm #2 Part C) and in combination with alpelisib (Arm #3 Part F), everolimus (Arm #4 Part H) and abemaciclib (Arm #5 Part J). • To characterize the PK profile of amcenestrant administered as monotherapy (Arm#1), or in combination in each study Arms, as well as the PK profile of palbociclib, alpelisib, everolimus and abemaciclib in the appropriate treatment arm. • To evaluate the antitumor activity using **ORR** according to RECIST v1.1 of amcenestrant administered as monotherapy (Arm #1 Part A), in combination with palbociclib (Arm #2 Part C and D), in combination with alpelisib (Arm #3 Part F and G), in combination with everolimus (Arm #4 Parts H and I), and in combination with abemaciclib (Arm #5 Parts J and K), the clinical benefit rate (**CBR**) defined as complete response [CR], partial response [PR] and stable disease [SD] ≥24 weeks, and progression-free survival (**PFS**) in each treatment arm. • To evaluate the ORR and CBR (CR, PR and SD ≥24 weeks) in dose expansion of each study treatment arm according to the estrogen receptor 1 (ESR1) gene mutational status (mutant and wild type) at baseline and during treatment. • To evaluate the time to first tumor response (CR or PR) in dose expansion of each study treatment arm. • To evaluate residual ER availability with positron emission tomography (PET) scan [(18)F] fluoroestradiol (^{18}F-FES) uptake with increasing doses of amcenestrant (Arm #1 Part A). • To assess the food effect on PK of amcenestrant (Arm #1 Part A). • To assess potential induction/inhibition effect of amcenestrant on cytochrome P450 (CYP) 3A using 4b-OH cholesterol (ie, full PK sampling for Arm #1 Parts A and B, Arm#5 Parts J and K) **Exploratory objectives** • To evaluate PK/pharmacodynamic (PD) relationships. • To evaluate target engagement: confirm the ER degradation with re-biopsy of the tumor at recommended dose in Arms #1 (Part B), #3 (Parts F,G), #4 (Parts H,I), and #5 (Parts J, K). • To evaluate other breast cancer biomarkers in tumor over time such as Ki67, Bcl-2, PgR, ER and tumor gene expression profiles in Arms #1 (Parts A, B), #3 (Parts F, G), #4 (Parts H, I), and #5 (Parts J, K). In Arm #5 (Parts J, K), Cyclin D1 protein expression will be evaluated too, at baseline and over time. Results will be correlated with patients' clinical parameters. • To assess the extent of metastases with FDG PET/CT during dose escalation (Arm #1 Part A BID). • To evaluate change of cfDNA alterations from screening to progression of disease during Arm #1 (Part B), #2, #3, #4, and #5. The percentage of patients with cfDNA alterations will be provided over time to characterize the biological evolution of the disease in each patient. The association of these alterations with clinical outcomes will also be provided.

STUDY DESIGN	This is an open-label, non-comparative, dose escalation and dose expansion, safety, efficacy, PK, and PD evaluation study of amcenestrant administered orally as monotherapy (Parts A and B) and in the following combinations: with palbociclib (Parts C and D), alpelisib (Parts F and G), everolimus (Parts H and I) and abemaciclib (Parts J and K). This study will be performed in 10 parts (5 Arms), in postmenopausal women with ER-positive and HER2-negative advanced breast cancer: ***Arm #1 Part A*** Dose escalation study to evaluate the safety, PK and PD of amcenestrant administered as monotherapy, including pilot food effect sub-study. ***Arm #1 Part B*** Dose expansion study to evaluate the efficacy, safety, PK and PD of amcenestrant administered at the RD (from Part A). ***Arm #2 Part C*** Dose escalation study to evaluate the safety, PK and PD of amcenestrant administered in combination with the recommended standard dosage of palbociclib. ***Arm #2 Part D*** Dose expansion study to characterize the overall safety, anti-tumor activity PK and PD of amcenestrant administered at the selected dose(s) (from Part C) in combination with palbociclib. ***Arm #3 Part F*** Safety run-in phase to evaluate the safety, PK and PD of amcenestrant administered in combination with the recommended standard dosage of alpelisib. ***Arm #3 Part G*** Dose expansion study to characterize the overall safety, anti-tumor activity PK and PD of amcenestrant administered at the RD dose (from Part F) in combination with alpelisib ***Arm #4 Part H*** Dose escalation study to evaluate the safety, PK and PD of amcenestrant administered in combination with everolimus. ***Arm #4 Part I*** Dose expansion study to characterize the overall safety, anti-tumor activity PK and PD of amcenestrant administered at the confirmed RD dose (from Part H) in combination with everolimus. ***Arm #5 Part J*** Dose escalation study to evaluate the safety, PK and PD of amcenestrant administered in combination with abemaciclib. ***Arm #5 Part K*** Dose expansion study to characterize the overall safety, anti-tumor activity PK and PD of amcenestrant administered at the confirmed RD dose (from Part J) in combination with abemaciclib. A Study Committee will be set up, which will include the investigators (or designee) who participate in dose escalation study parts, Sponsor representatives, and, if needed, the ad-hoc experts (eg, FES PET expert). The Study Committee will meet regularly during the dose escalation/safety run-in study parts. The Study Committee will review available clinical data including PK and safety data (especially DLTs) as well as FES-PET scan results for Arm#1 Part A of each individual patient who are treated in dose escalation study parts in

order to adjust the number of enrolled patients at each dose level, as well as to decide the further dose escalation, if appropriate. Decisions regarding final dose selection will be made at the Dose Selection meeting which will be documented and shared with sites.

Arm #1

A) Dose escalation of amcenestrant monotherapy (Part A)

Dose escalation will be initiated with a once daily (QD) schedule with a starting dose of 20 mg/day. Dose escalation is expected to proceed according to the table below. Intra-patient dose escalation or re-escalation will not be permitted.

Amcenestrant dose levels in Part A

Dose level (DL)[a]	Amcenestrant (mg)
DL(-1) QD	*10 once daily*
DL1 QD	*20 once daily*
DL1bis QD	*50 once daily*
DL2 QD	*100 once daily*
DL2bis QD	*150 once daily*
DL3 QD	*200 once daily*
DL4 QD	*400 once daily*
DL4bis BID[b]	*200 twice daily*
DL5 QD	*600 once daily*
DL5bis BID[b]	*300 twice daily*

a Additional intermediate or higher dose levels can be tested after agreement between Sponsor and Investigators (Study Committee)

b A BID schedule of administration may be added during the study, the starting dose will be a DL of the same dose intensity as the highest cleared DL with QD Schedule. Other schedules of administration may be added during the study.

Part A of this study is designed using the 3 + 3 concept; 3 to 6 patients will be treated at each dose level depending on DLTs observed in the first 3 patients. If one of the first 3 evaluable patients experiences DLTs during Cycle 1, this cohort will be expanded with a total of up to 6 patients. If less than 1 out of 3 patients or less than 2 out of 6 patients experienced DLTs at a given dose level, the dose escalation will proceed to the next dose level.

In addition, ^{18}F-FES-PET scan results should be available for all DLT evaluable patients in Part A and depending on results at DL1 and DL2, the intermediate dose levels (DL1bis and DL2bis) could be explored (see Section 6.2.1). From these two dose levels DL1bis and DL2bis, the next dose levels (DL2 and DL3 respectively) should not be skipped.

At subsequent dose levels (≥DL3), other intermediate or higher dose levels may be tested based on safety, ^{18}F-FES-PET scan results (if all patients have >90% of inhibition of the target) and PK parameters upon recommendation from the Study Committee.

The second and third patients of a given cohort can only be enrolled when the first patient will have received at least 1 week of amcenestrant without DLT. The enrollment at the next dose level may not proceed before at least 3 patients treated at the current dose level have been followed for at least 1 cycle duration (ie, 28 days) and are evaluable for DLT assessment.

Patients who discontinue study treatment prematurely before the end of DLT observation period for any reason other than DLT must be replaced.

	As a rule, the dose escalation part will stop when the maximum administered dose (MAD) is reached, MAD being defined as the dose at which ≥33% (2 patients out of up to 6) of evaluable patients have experienced a DLT at Cycle 1. The MTD is defined as the highest dose level at which no more than 1 patient of a maximum of 6 patients experienced a DLT. Usually, the MTD is one dose level below the MAD or the highest dose tested if the MAD is not reached. Although dose escalation process is guided by the safety evaluation during Cycle 1 of treatment, cumulative or irreversible toxicities observed after subsequent administrations should also be considered for the dose escalation and the dose selection decisions (ie, expansion of a given dose level, intermediate dose levels), as well as any other relevant information, upon recommendation from the Study Committee. The RD for the expansion cohorts will be primarily based on safety data, but also on target saturation, PK and PK/PD data. If the MTD cannot be determined in the absence of DLTs at the MAD, the following will also be taken into account for the RD selection and the decision to expand the study to other dose expansion study parts: PK after repeated administration, level of inhibition of target occupancy measured by ^{18}F-FES-PET imaging, PK/PD on ER occupancy and any other relevant information. The RD should be potentially at least 2 dose levels above the dose level showing >90% of inhibition of the target on ^{18}F-FES-PET scan at this dose level, unless there are DLTs at this dose, in which case the RD could be any dose where >90% inhibition was reached. The twice a day (BID) regimen will be explored on 6 DLT-evaluable patients at the dose level providing the same dose intensity as the highest cleared QD dose level (600 mg): 300 mg taken two times a day 12 hours apart (ie, 2 x 300 mg ±1 hour). Other doses such as 200 mg taken two times a day 12 hours apart may be explored. In that case, 6 DLT-evaluable patients will be enrolled at this dose level. ***Pilot food effect***: A pilot food effect will be assessed by PK sampling after drug administration with a standard meal on Day 3 of Cycle 1 in all patients treated in Part A. All other dosing in Part A will be taken in fasted condition. If results from the QD dosing regimen allow conclusions to be drawn, this will not be implemented for other dosing regimens (eg, BID) that are explored. **B) Dose Expansion of amcenestrant monotherapy (Part B)** When the dose escalation phase ends for the QD regimen, the RD will be proposed by the Study Committee for the expansion cohort (Part B) and a total of 78 patients will be treated at this RD. Intra-patient dose escalation or re-escalation is not allowed. An interim analysis based on ORR (by RECIST v1.1) is planned when 45 patients are treated in order to decide, based on preset criteria, if the recruitment of planned additional patients is justified (see statistical considerations). If results in Part A with the BID dosing regimen are of interest in terms of safety, PK, exposure, preliminary efficacy and any other relevant information such as data from patients treated with the QD regimen, and warrants further investigation, a BID regimen could be tested in an additional expansion subpart with a total of 56 patients treated at the recommended BID regimen from Part A. In that case, an interim analysis based on ORR (by RECIST v1.1) would be planned when 29 patients are treated in order to decide, based on preset criteria, if the recruitment of planned total patients is justified.

Arm #2 – amcenestrant in combination with palbociclib

C) Dose Escalation (Part C)

It is expected to assess 2 amcenestrant dose levels schedule starting from one dose level below the RD fixed in Part A (RD[A-1]) and then amcenestrant (RD[A]), using the 3 + 3 standard dose escalation design with palbociclib given at fixed dose. The Study Committee will decide on whether to escalate (or not) to the next amcenestrant dose level in combination with palbociclib during Study Committee meetings on the basis of their knowledge of the whole safety profile, and PK results.

Amcenestrant dose levels in Part C

Dose levels (DL)[a]	Amcenestrant	Palbociclib[b]
DL1 QD	DL RD(A-QD)-1	125 mg
DL2 QD	RD(A-QD)	125 mg
DL3 BID	RD(A-BID)	125 mg

a Lower dose, intermediate dose levels and a BID dose regimen can be tested after agreement between Sponsor and Investigators (Study Committee)

b Oral route once daily with food for 21 days followed by 7 days off therapy to comprise a complete cycle of 28 days. Lower dose (eg, 100 mg, 75 mg) can be proposed depending on tolerance

Three to 6 evaluable patients will be treated at each dose level, and dose escalation decision will be based on DLT observed for at least 1 cycle duration (ie, 28 days) of the first 3 evaluable patients. If one of the first 3 evaluable patients experiences DLT during Cycle 1, this cohort will be expanded with a total of 6 patients. If none of the first 3 patients or less than 2 out of 6 patients experienced a DLT, the dose escalation will proceed to the next dose level. The second and third patients of a given cohort can only be enrolled when the first patient will have received 1 week of amcenestrant and palbociclib without DLT. The enrollment at the next dose level may not proceed before at least 3 patients treated at the current dose level have been followed for at least 1 cycle duration (ie, 28 days) and are evaluable for DLT assessment.

Patients who discontinue study treatment prematurely before the end of DLT observation period for any reason other than DLT must be replaced.

As a rule, the dose escalation will stop when the MAD, dose at which ≥33% (2 patients out of up to 6) of evaluable patients have experienced a DLT at Cycle 1, is reached. The MTD is defined as the highest dose level at which no more than 1 patient of a maximum of 6 evaluable patients experienced a DLT. The MTD is one dose level below the MAD or the highest dose tested if MAD is not reached. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

Although the dose escalation process is guided by the safety evaluation during Cycle 1 of treatment, cumulative or irreversible toxicities observed after subsequent administrations will also be considered for the dose escalation and the dose selection decisions (ie, expansion of a given dose level, intermediate dose levels), as well as any relevant information, upon recommendation from the Study Committee.

D) Dose Expansion (Part D)

When the dose escalation phase (Part C) ends, at least one RD will be proposed by the Study Committee for the expansion cohort (Part D) and approximately 28 patients will be treated at each selected RD (from Part C). Intra-patient dose escalation or re-escalation of any study drug is not allowed. The Study Committee will review preliminary data (eg, safety, efficacy and PK) of each selected RD.

Arm #3 – amcenestrant in combination with alpelisib

E) Safety Run-In (Part F)

Amcenestrant 200 mg QD dose level will be assessed in combination with alpelisib at a fixed (standard) dose of 300 mg per alpelisib label according to incidence of DLTs and PK results. Additional dose levels of amcenestrant (eg, 300 mg QD, or 400 mg QD, or 100 mg BID, or 200 mg BID etc.) with alpelisib could be explored if needed based on the safety and PK results from the 200 mg dose level testing with 300 mg alpelisib. Lower dose of alpelisib (eg, 250 mg or 200 mg) could be explored from Cycle 1 Day 1 based on the PK results and safety profile from the initial combination of amcenestrant 200 mg and alpelisib 300 mg on the first 3 to 6 patients in Part F.

Based on the preliminary safety profile as well as PK and preliminary antitumor activity data, the Study Committee will decide whether to test additional amcenestrant dose levels in the safety run-in part and expand the alpelisib combination to Part G, or not.

Amcenestrant and alpelisib dose levels in Part F[a]

Dose levels (DL)[b]	Amcenestrant	Alpelisib Standard dose[c]	Alpelisib (reduced dose)[d]
DL1 QD	200 mg	300 mg	
DL2 QD	200 mg		250 mg
DL3 QD	200 mg		200 mg

a In Part F (and G), Cycle 1 is defined as a 28-day cycle with 3 days of pretreatment with alpelisib single-agent for PK assessment followed by a 25-day treatment cycle with amcenestrant and alpelisib. Following cycles will also continue to be 28 days.

b Lower or higher doses QD, and BID dose regimen can be tested after agreement between Sponsor and the Study Committee

c Oral route, once daily with food.

d Lower dose (eg, 250 mg, 200 mg) can be proposed depending on tolerance

Up to 6 DLT-evaluable patients could be treated at the already established amcenestrant dose of 200 mg when given in combination with other drugs, in order to confirm this dose when administered in combination with alpelisib. Lower dose levels of alpelisib and/or other dose levels of amcenestrant could be considered for testing in Part F if this established dose is not confirmed.

A decision to continue to dose expansion study part (Part G) will be based on DLTs observed for at least 1 cycle duration of all evaluable patients, and PK results from Part F combination. Intra-patient dose escalation or re-escalation of any study drug is not allowed

1) If none or one of the first 3 evaluable patients experiences DLT(s) during Cycle 1, the cohort will be expanded to include an additional 3 patients for a total of 6 patients.
   a) In the second set of 3 patients (ie, 6 patients altogether), if none or one DLT is experienced among the 6 patients (ie, 0/6 or 1/6), the doses of the combination are adequate for further testing in Part G.
   b) In the second set of 3 patients (ie, 6 patients altogether), if two or more DLTs are experienced among the 6 patients (ie, ≥2/6), the doses of the combination are NOT adequate for further testing in Part G. In this case, other dose levels of alpelisib and/or amcenestrant could be considered in Part F, or Part F can be stopped.
2) If 2 or more of the first 3 evaluable patients experience DLT(s), lower dose of alpelisib dose and/or other dose levels of amcenestrant will be considered or a decision to stop Part F can be made.

Although the confirmation of amcenestrant dose when given in combination with alpelisib will be guided by safety evaluation during Cycle 1, cumulative or irreversible toxicities observed after subsequent administrations will also be considered for dose selection/confirmation decision (ie, expansion of a given dose level), as well as any relevant information such as PK and anti-tumor activity data that may need additional patients, upon recommendation from the Study Committee.

F) Dose Expansion (Part G)

When the safety run-in (Part F) completes, based on safety, PK and efficacy data, RD of amcenestrant for the combination therapy will be confirmed by Study Committee for expansion cohort (Part G), and approximately 34 patients will be treated at the amcenestrant confirmed RD from Part F agreed by the Study Committee. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

Arm #4 – amcenestrant in combination with everolimus

G) Dose escalation (Part H)

Amcenestrant 200 mg QD dose level will be assessed in combination with everolimus two dose levels: 5 mg QD and 10 mg QD based on the incidence of DLT(s) and PK results. In this dose escalation part, additional dose levels of amcenestrant (eg, 300 mg QD, or 400 mg QD, or 100 mg BID, or 200 mg BID etc.) with everolimus could also be explored if needed, based on the safety and PK results of everolimus in this dose escalation study.

Based on the preliminary safety profile, PK and antitumor activity data, Study Committee will determine the recommended dose (RD) of everolimus in combination with amcenestrant 200 mg QD, and/or expand this combination to Part I, or not.

Amcenestrant and everolimus dose levels in Part H[a]

Dose levels (DL)	Amcenestrant[b]	Everolimus[c] (QD)
DL1 QD	200 mg	5 mg
DL2 QD	200 mg	10 mg[d]

a In Part H, Cycle 1 is defined as a 28-day treatment cycle of amcenestrant and everolimus. Following cycles will also continue to be 28 days.
b Lower or higher doses QD, and BID dose regimen can be tested after agreement between Sponsor and Study Committee
c Oral route, once daily (QD) with food.
d Lower dose of everolimus, (5 mg QOD (every other day) can be explored depending on tolerance

Six (6) to 12 evaluable patients will be treated with already established RP2D of amcenestrant dose of 200 mg QD when given in combination with 2 dose levels of everolimus: 5 mg QD and 10 mg QD. Dose escalation decision will be based on DLT(s) observed for at least 1 cycle duration (ie, 28 days) in a following way:

- If 1 of the first 3 evaluable patients who were treated with amcenestrant 200 mg QD and everolimus 5 mg QD experienced DLT(s) during Cycle 1, this cohort will be expanded with 3 additional patients at the same dose level of everolimus and amcenestrant to the total of 6 patients.
- If 0 of the first 3 patients or less than 2 out of 6 patients treated at amcenestrant 200 mg QD with 5 mg everolimus QD experienced DLT(s), dose escalation will proceed to the next dose level of everolimus (ie,10 mg QD) and amcenestrant 200 mg QD by adding

	3 patients at this new combination dose level, to the total of 6 or 9 patients. • If 1 of the first 3 evaluable patients treated with amcenestrant 200 mg QD and everolimus 10 mg QD experienced DLT(s) during Cycle 1, this cohort will be expanded with 3 additional patents to total of 9 or 12 patients in dose escalation study. The second and third patients of a given cohort can only be enrolled when the first patient will have received 1 week of amcenestrant and everolimus without experiencing DLT(s). The enrollment at the next dose level of everolimus may not proceed to 10 mg QD dose level before at least 3 patients treated with amcenestrant 200 mg QD and everolimus initial dose level (5 mg QD) have been followed for at least 1 cycle duration (ie, 28 days) and are evaluable for DLTs' assessment. Patients who discontinue study treatment prematurely before the end of DLT observation period for any reason other than DLT(s) must be replaced. As a rule, the dose escalation will stop when the MAD, dose at which ≥33% (2 patients out of up to 6) of evaluable patients have experienced a DLT at Cycle 1, is reached. The MTD is defined as the highest dose level at which no more than 1 patient of a maximum of 6 evaluable patients experienced DLT(s). The MTD is one dose level below the MAD or the highest dose tested if MAD is not reached. Intra-patient dose escalation or re-escalation of any study drug is not allowed. Although the dose escalation process is guided by the safety evaluation during Cycle 1 of treatment, cumulative or irreversible toxicities observed after subsequent administrations will also be considered for dose escalation, dose selection decisions (ie, expansion of a given dose level, intermediate dose levels), as well as any relevant information, upon recommendation from the Study Committee. **H) Expansion cohort (Part I)** When the dose escalation study (Part H) completes, based on safety, PK and preliminary antitumor activity data, RD of everolimus for the combination therapy will be proposed by Study Committee for expansion cohort (Part I); approximately 12 patients will be treated at the RD from Part H selected by the Study Committee. Intra-patient dose escalation or re-escalation of any study drug is not allowed. **<u>Arm #5 – amcenestrant in combination with abemaciclib</u>** **I) Dose Escalation (Part J)** Amcenestrant 200 mg QD dose level will be assessed in combination with abemaciclib two dose levels: 100 mg BID and 150 mg BID according to incidence of DLT(s) and PK results. Additional dose levels of amcenestrant (eg, 300 mg QD, or 400 mg QD, or 100 mg BID, or 200 mg BID etc.) with abemaciclib could be explored if needed based on the safety and PK results from this dose escalation study. Based on the preliminary safety profile, PK and preliminary antitumor activity data, the Study Committee will determine the recommended dose (RD) of abemaciclib in combination with amcenestrant 200 mg QD, and/or expand this combination to Part K, or not.

Amcenestrant and abemaciclib dose levels in Part J[a]

Dose levels (DL)	Amcenestrant[b]	Abemaciclib[c] (BID)
DL1 QD	200 mg QD	100 mg BID[d]
DL2 QD	200 mg QD	150 mg BID

a In Part J, Cycle 1 is defined as a 28-day treatment cycle of amcenestrant and abemaciclib. Following cycles will also continue to be 28 days.
b Lower or higher doses QD and BID dose regimen can be tested after agreement between Sponsor and Study Committee
c Oral route, twice daily (BID) with food.
d Lower doses of abemaciclib, 50 mg BID can be used depending on tolerance

Six (6) to 12 evaluable patients will be treated with already established RP2D of amcenestrant dose of 200 mg QD when given in combination with 2 dose levels of abemaciclib: 100 mg BID and 150 mg BID. Dose escalation decision will be based on DLT(s) observed for at least 1 cycle duration (ie, 28 days) in a following way:

- If 1 of the first 3 evaluable patients who were treated with amcenestrant 200 mg QD and abemaciclib 100 mg BID experienced DLT(s) during Cycle 1, this cohort will be expanded with 3 additional patients at the same dose level of abemaciclib and amcenestrant to the total of 6 patients.
- If 0 of the first 3 patients or less than 2 out of 6 patients treated at amcenestrant 200 mg QD with abemaciclib 100 mg BID experienced DLT(s), dose escalation will proceed to the next dose level of abemaciclib (ie,150 mg BID) and amcenestrant 200 mg QD by adding 3 patients at this new combination dose level, to the total of 6 or 9 patients
- If 1 of the first 3 evaluable patients treated with amcenestrant 200 mg QD and abemaciclib 150 mg BID experienced DLT(s) during Cycle 1, this cohort will be expanded with 3 additional patents to total of 9 or 12 patients in dose escalation study.

The second and third patients of a given cohort can only be enrolled when the first patient will have received 1 week of amcenestrant and abemaciclib without experiencing DLT(s).

The enrollment at the next dose level of abemaciclib may not proceed to 150 mg BID dose level before at least 3 patients treated with amcenestrant 200 mg QD and abemaciclib initial dose level (100 mg BID) have been followed for at least 1 cycle duration (ie, 28 days) and are evaluable for DLTs' assessment.

Patients who discontinue study treatment prematurely before the end of DLT observation period for any reason other than DLT(s) must be replaced.

As a rule, the dose escalation will stop when the MAD, dose at which ≥33% (2 patients out of up to 6) of evaluable patients have experienced a DLT at Cycle 1, is reached. The MTD is defined as the highest dose level at which no more than 1 patient of a maximum of 6 evaluable patients experienced DLT(s). The MTD is one dose level below the MAD or the highest dose tested if MAD is not reached. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

Although the dose escalation process is guided by the safety evaluation during Cycle 1 of treatment, cumulative or irreversible toxicities observed after subsequent administrations will also be considered for dose escalation, dose selection decisions (ie, expansion of a given dose level, intermediate dose levels), as well as any relevant information, upon recommendation from the Study Committee.

	J) Dose expansion (Part K) When the dose escalation study (Part J) completes, based on safety, PK and preliminary antitumor activity data, RD of abemaciclib for the combination therapy will be proposed by Study Committee for expansion cohort (Part K); approximately 20 patients will be treated at the RD from Part J selected by the Study Committee. Intra-patient dose escalation or re-escalation of any study drug is not allowed.
STUDY POPULATION **Main selection criteria**	***Inclusion criteria:*** I 01. Patients must be postmenopausal women as defined by one of the following: a) Women >60 years b) Women ≤60 years: - With spontaneous cessation of menses >12 months prior to registration in the absence of chemotherapy, tamoxifen and toremifene. - Or with cessation of menses of duration ≤12 months or secondary to hysterectomy AND have follicle stimulating hormone (FSH) level in the postmenopausal range according to institutional standards (or >34.4 IU/L if institutional range is not available) prior to registration. - Or who have received hormonal replacement therapy but who have discontinued this treatment AND have FSH level in the postmenopausal range according to institutional standards (or >34.4 IU/L if institutional range is not available) prior to registration. - Or with status post bilateral surgical oophorectomy. - Or are premenopausal women on a gonadotropin-releasing hormone (GnRH) analog for at least 6 months (to be continued during study treatment) and have a negative pregnancy test prior to initiation of study treatment and at monthly intervals during treatment. In Arm #3 (Parts F and G) only, patients and their male partners must agree to use non-oral contraception if sexually active during the treatment and 1 week after the last dose. In Arm #4 (Parts H and I) only, patients and their male partners must agree to use non-oral contraception if sexually active during the treatment and 8 weeks after the last dose. In Arm #5 (Parts J and K) only, patients and their male partners must agree to use non-oral contraception if sexually active during the treatment and 3 weeks after the last dose. I 02. Patients with histological or cytological proven diagnosis of the breast adenocarcinoma with evidence of either locally advanced not amenable to radiation therapy or surgery in a curative intent, inoperable and/or metastatic disease. I 03. Either the primary tumor or any metastatic site must be positive for ER (>1% tumor cell staining by immunohistochemistry (IHC). I 04. Either the primary tumor or any metastatic site must be HER2 non-overexpressing by IHC (0, 1+) or in situ hybridization-negative based on single-probe average HER2 copy number <4.0 signals/cell or dual-probe HER2/ centromeric probe for chromosome 17 (CEP17) ratio <2 with an average HER2 copy number <4.0 signals/cell as per the American Society of Clinical Oncology guidelines.

	I 05.	Prior chemotherapy for advanced disease is allowed. **Prior chemotherapy for advanced disease is not allowed in dose expansion of Arms #3, #4, and #5 (Part G, I and K respectively).** (Note: Antibody drug conjugates [ADCs] are considered as chemotherapy in the study): - Patients must have received no more than 3 prior chemotherapeutic regimens in Arm #1 Part A (dose escalation, monotherapy). - Patients must have received no more than 1 prior chemotherapeutic regimen in Arms #1, #2, #3, #4, and #5 (Parts B, C, D, F, H and J respectively)
	I 06.	Patients must have received at least 6 months of prior endocrine therapy for advanced breast cancer. **Dose Escalation study parts:** Arm #3: - **Part F**: up to 2 prior lines of either single endocrine therapy and/or endocrine-based therapy Arm #4: - **Part H**: up to 2 prior lines of either single endocrine therapy and/or endocrine-based therapy (exemestane not allowed) Arm #5: - **Part J**: up to 2 prior lines of either single endocrine therapy and/or endocrine-based therapy **Dose Expansion study parts:** Arm #2: - **Part D**: no more than 2 prior lines of advanced endocrine therapy for advanced disease are allowed Arm #3: - **Part G**: patients must have received and progressed on the combination of Aromatase Inhibitors (AI) + CDK4/6 inhibitor as the first line (1L) treatment for advanced disease Arm#4: - **Part I**: patients must have received and progressed on the combination of Aromatase Inhibitors (AI) + CDK4/6 inhibitor as the first line (1L) treatment for advanced disease (exemestane not allowed) Arm#5: - **Part K**: up to 1 prior line of a single endocrine therapy for advanced disease **Note**: Additional patients who relapsed while on previous adjuvant endocrine therapy that was initiated ≥24 months ago, OR relapsed <12 months after completion of adjuvant endocrine therapy are also allowed for Arms #2, #3, #4, and #5 (Parts C, D, F, G, H, I, J and K)
	I 07.	Age ≥18 years old.
	I 08.	Measurable lesion by RECIST v1.1.
	I 09.	The patient is capable of understanding the informed consent and complying with the protocol and has signed the informed consent form (ICF) before any study (specific screening procedures or evaluations).
	Arm #1 Part A only	
	I 10.	Patient entering Part A must agree to undergo: c) Two ^{18}F-FES-PET/computerized tomography (CT) imaging scans, one at baseline and one between Day 11 and Day 15 of study treatment intake, and d) Two FDG PET/CT for Part A BID, one at baseline and one between Day 11 and Day 15 of study treatment intake before ^{18}F-FES-PET (patients whose baseline FDG PET/CT results are negative for tumors will not be eligible), and e) Paired biopsies (before treatment and during treatment): For baseline samples, formalin-fixed and paraffin-embedded (FFPE)

	archived biopsy samples (within past 3 months prior initiation of study treatment) can be used, but preferably fresh biopsies from primary tumor or recurrence or metastasis, will be collected. It is recommended that the end of Cycle 2 on-treatment biopsy be collected at the same location as the baseline biopsy, whenever the tumor is accessible for a biopsy during treatment. **Arm #1 Part B** I 11. For patients who consent to paired biopsies (before treatment and during treatment): for baseline samples, FFPE archived biopsy samples can be used (within past 3 months prior to initiation of study treatment), but preferably fresh biopsies from primary tumor or recurrence or metastasis will be collected. It is recommended that the end of Cycle 2 on-treatment biopsy be collected at the same location as the baseline biopsy, whenever the tumor is accessible for a biopsy during treatment. **Arm #3 Part F and G only** I 12. In Parts F and G, patient must have confirmed/detected *PIK3CA* mutations determined in tumor tissue and/or plasma cfDNA. The *PIK3CA* testing should be performed locally. ***General exclusion criteria related to study methodology*** E 01. Eastern Cooperative Oncology Group (ECOG) performance status ≥2. E 02. Significant concomitant illness, including psychiatric condition that, in the opinion of the Investigator or Sponsor, would adversely affect the patient's participation in the study. E 03. Medical history or ongoing gastrointestinal disorders potentially affecting the absorption of oral IMPs. Patients unable to swallow normally and to take capsules. Predictable poor compliance to oral treatment. E 04. Any malignancy related to human immunodeficiency virus (HIV); or unresolved viral hepatitis. E 05. Patients with a life expectancy less than 3 months. E 06. Patient not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or patients potentially at risk of noncompliance to the study procedures (ie, unwillingness and inability to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions). E 07. Major surgery within 4 weeks prior to first study treatment administration. E 08. Patient with any other cancer. However, adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer or any other cancer from which the patient has been disease free for >3 years are allowed. E 09. Patient is the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff or relative thereof directly involved in the conduct of the protocol. **Arm #1 Part A only** E 10. Patient with liver metastases only.

	Exclusion criteria related to the disease E 11. Patients with known brain metastases, leptomeningeal carcinomatosis or/and spinal cord compression. Patients with brain metastases that have been previously totally resected or irradiated are eligible provided no progression or relapse is observed within 4 weeks of the treatment E 12. Treatment with anticancer agents (including investigational drugs) less than 2 weeks before first study treatment administration (less than 4 weeks if the anticancer agents were antibodies). E 13. Prior treatment with another selective ER down-regulator (SERD): - Dose Escalation study parts **(Parts F, H and J)**: SERDs are not allowed except for fulvestrant which will need a washout of at least 6 weeks prior to the first study drug administration. - Dose Expansion study parts **(Parts G, I and K)**: prior (last) treatment with any SERD including fulvestrant will not be allowed. E 14. Inadequate hematological function including neutrophils <1.5 x 10^9/L; platelet count <100 x 10^9/L. E 15. Prothrombin time: International normalized ratio(INR) >1.5 times the upper limit of normal (ULN) or out of therapeutic range if receiving anticoagulation that would affect the PT/INR. E 16. Inadequate renal function with serum creatinine ≥1.5 x ULN or, if between 1.0 and 1.5 x ULN with eGFR <60 mL/min/1.73 m^2 as estimated using the abbreviated Modification of Diet in Renal Disease formula (Appendix I). E 17. Liver function: aspartate aminotransferase (AST) >3 x ULN, or alanine aminotransferase (ALT) >3 x ULN. Alkaline phosphatase (ALP) up to Grade 2 (2.5 to 5 X ULN), gamma glutamyl transferase (GGT) up to Grade 2 (2.5 to 5 X ULN) would be acceptable only if related to the presence of bone and/or liver metastases as judged by the Investigator. Total bilirubin >1.5 x ULN. E 18. Patients with Gilbert disease. E 19. Non-resolution of any prior treatment related toxicity to < Grade 2, except for alopecia according to National Cancer Institute Common Terminology Criteria for adverse events (NCI-CTCAE) v4.03 (Appendix B). E 20. E20 criterion removed per amendment 10 E 21. a. All study parts, treatment with strong CYP3A inducers within 2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest (see Appendix E). b. For Arm#1 (Part A and B) and Arm#5 (Part J and K, full PK sampling only), in patients with 4βOH cholesterol assessment: Treatment with strong and moderate CYP3A inhibitors within 2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest (see Appendix E). E 22. More than 1 prior advanced CDK4/6 inhibitor-based therapy in Arm #1, Arm #2 (Part C), Arm #3 (Parts F and G), and Arm#4 (Part H). E 23. Treatment with strong CYP3A inhibitors within 2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest in Arm#2 (Parts C and D) only according to palbociclib labeling (see Appendix E).

	E 24. Medical conditions requiring concomitant administration of medications with a narrow therapeutic window metabolized by CYP3A and for which a dose reduction cannot be considered in Arm #2 (Part C and D) according to palbociclib labeling (see Appendix F). E 25. Arm #2 (Part D) and Arm #5 (Parts J, and K) only: Prior therapy with targeted therapy for advanced disease (ie, CDK 4/6 inhibitors, PI3K inhibitors, mTOR inhibitors and AKT inhibitor). **Part E (Canceled per Amendement 08)** The following exclusion criteria are specfic for patients enrolled in the drug-drug interaction sub-study E 26. E26 criterion removed per Amendment 08. E 27. E27 criterion removed per Amendment 08. E 28. E28 criterion removed per Amendment 08. E 29. E29 criterion removed per Amendment 08. E 30. Arm #2, #3, #4 and #5 (Parts C, D, F, G, H, I, J and K) only: Patients with concurrent or history of pneumonitis E 31. Arm #3, #4 and #5 (Parts F, G, H, I, J and K) only: prior treatment therapies that target the PI3K axis (mTOR inhibitors, AKT inhibitors, PI3K inhibitors) E 32. Arm #3 and #4 (Parts F, G, H and I) only: Patients with Diabetes Mellitus type-I or uncontrolled Diabetes Mellitus type-II: ie, fasting plasma glucose ≥140 mg/dL (7.7 mmol/L) or HbA1C >6.2% E 33. Arm #3 and #4 (Parts F, G, H and I) only: History of severe cutaneous reaction (eg. Stevens-Johnson syndrome [SJS], erythema multiforme [EM), Toxic epidermal necrolysis (TEN), and Drug reaction with eosinophilia and systemic symptoms [DRESS]. E 34. Arm #3 (Parts F and G) only: Ongoing osteonecrosis of jaw **New Exclusion Criteria added in Amendment 09** E 35. Arm #4 (Parts H and I) only: Any active, untreated or uncontrolled infection (eg, viral, bacterial, fungal etc.) E 36. Arm #4 (Parts H and I) only: Patients with active and uncontrolled Stomatitis, Angioedema due to concomitant treatment with ACE Inhibitors, impaired wounds E 37. Arm #4 (Parts H and I) only: Uncontrolled Hypercholesterolemia, Hypertriglyceridemia and Hyperglycemia in non-diabetic patients E 38. Arm #4 (Parts H and I) only: Treatment with strong or moderate CYP3A4 inhibitors, strong CYP3A4 inducers and/or P-gp inhibitors within 2 weeks before the first study treatment administration or 5 elimination half-lives, whichever is the longest E 39. Arm #5 (Parts J and K) only: History or current (controlled/not controlled) Venous Thromboembolism (ie, Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), Cerebral Venous Sinus Thrombosis (CVST) **New Exclusion Criterion added in Amendment 10** E 40. Treatment with drugs that are sensitive substrate of OATP1B1/1B3 (eg, asunaprevir, atorvastatin, bosentan, danoprevir, fexofenadine, glyburide, nateglinide, pitavastatin, pravastatin, repaglinide, rosuvastatin and simvastatin acid) within 5 days before first study treatment administration or 5 half-lives whichever is longer, and in which this drug cannot be replaced.

Total expected number of patients	Up to approximately 251 patients (see statistical considerations)
Expected number of sites:	Approximately 40 sites overall
STUDY TREATMENT(s) **Investigational medicinal product** **Formulation** **Route of administration**	 Amcenestrant (SAR439859) 100 mg capsules Oral route
Dose regimen	In Arm #1 **Part A**, amcenestrant will be administered at assigned dose levels, within a 28-day cycle. For the QD regimen, during Cycle 1, one dose will be taken on Day 1 in fasting condition, no dose on Day 2 and repeated administration will start from Day 3. On Day 3 only, the dose will be taken in fed condition for a food effect evaluation, and then all subsequent administrations will be taken in fasted condition, and at approximately the same time each day (±3 hours). From the conclusions drawn with the initial QD dose regimen, patients treated with other dose regimens will be allowed to take amcenestrant in fasted or fed condition. For the BID regimen, the 600 mg dose will be split in two drug administrations: 300 mg taken two times a day 12 hours apart (ie, 2 x 300 mg) ±1 hour with or without food (with one dose only taken in the morning on Day 1, no dose on Day 2 and then repeated BID dosing from Day 3). In Arm #1, **Part B**, amcenestrant will be taken QD from Day 1 (without omission on Day 2) at the RD fixed in Part A, within a 28-day cycle, either in a fasting or fed condition; and at approximately the same time each day (±3 hours). A BID regimen (without omission on Day 2) may also be explored if found to be needed. In Arm #2, **Parts C and D**, amcenestrant will be administered from Day 1 (without omission on Day 2) at assigned dose levels, within a 28-day cycle in fed condition, and at approximately the same time each day (±3 hours). Amcenestrant and palbociclib must be taken together, 5 minutes apart. Both IMPs must be taken with food, regardless of the order of intake. In Arm #3, **Parts F and G**, amcenestrant will be taken in fed condition QD from Cycle 1 Day 4 at 200 mg (or other amcenestrant doses) together with alpelisib 300 mg QD (or lower alpelisib doses) at approximately the same time each day (±3 hours) within a 28-day cycle. The days of PK assessment (ie, on C1D3 and C1D22) the drugs will have to be taken with a standard breakfast. In Arm #4, **Parts H and I**, amcenestrant will be taken in fed condition QD from Cycle 1 Day 1 at 200 mg (or other amcenestrant doses) together with everolimus 10 mg QD (or lower doses) at approximately the same time each day (±3 hours) within a 28-day cycle. The days of PK assessment (ie, on C1D1 and C1D22) the drugs will have to be taken together with a standard breakfast. In Arm #5, **Parts J and K**, amcenestrant will be administered QD and abemaciclib BID, both from Cycle 1 Day 1 at assigned dose levels, within a 28-day cycle in fed condition, and at approximately the same time each day (±3 hours). Amcenestrant and abemaciclib will be administered together during the morning. The days of PK assessment (ie, on C1D1 and C1D22) the drugs will have to be taken together with a standard breakfast. If a dose is vomited or omitted, the patient should not take the dose later or 2 doses at the next planned dose, and this information has to be recorded in the diary. Amcenestrant dose omission or reduction could occur in case of toxicity, as well as cycle delay in Arms #2, #3, #4, and #5 (see Section 6.5). Advise to avoid sun exposure and wear protective clothing, sunscreen, and lip balm with high sun protection (eg, SPF ≥30) when outdoors during study treatment and 5 days after the last amcenestrant administration.

Investigational medicinal product **Formulation** **Route of administration** **Dose regimen**	**Palbociclib (Ibrance®)** 125 mg, 100 mg and 75 mg capsules Oral route The RD of palbociclib is a 125 mg capsule taken once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib should be taken with food at approximately the same time each day. Dose omission or reduction could occur in case of toxicity, (see Section 6.5). If a dose is vomited or omitted the patient should not take the dose later or 2 doses at the next planned dosing, and this information has to be recorded in the diary.
Investigational medicinal product **Formulation** **Route of administration** **Dose regimen**	**Alpelisib** 50 mg and 200 mg Oral route The RD of alpelisib is 300 mg. In both study parts, Part F (refer to the dose per pharmacy manual) and in Part G (refer to the dose per pharmacy manual) tablets should be taken orally once daily with food at approximately the same time each day. Dose omission or reduction could occur in case of toxicity (see Section 6.5). If a dose is vomited or omitted the patient should not take the dose later or 2 doses at the next planned dosing, and this information has to be recorded in the diary.
Investigational medicinal product **Formulation** **Route of administration** **Dose regimen**	**Everolimus** 5 mg Oral route The RD of everolimus is 10 mg taken orally, once a day as 2x5 mg with food at approximately the same time each day. Dose omission or reduction could occur in case of toxicity, (see Section 6.5). If a dose is vomited or omitted the patient should not take the dose later or 2 doses at the next planned dosing, and this information has to be recorded in the diary.
Investigational medicinal product **Formulation** **Route of administration** **Dose regimen**	**Abemaciclib** 50 mg, 100 mg, and 150 mg tablet Oral route Abemaciclib will be taken orally, twice a day as 2x100 mg and/or 2x150 mg with food at approximately the same time each day. Dose omission or reduction could occur in case of toxicity, (see Section 6.5). If a dose is vomited or omitted the patient should not take the dose later or 2 doses at the next planned dosing, and this information has to be recorded in the diary.

ENDPOINT(S)	**Primary endpoint** Arms #1, #2, #3, #4, and #5 (***Part A, C, F, H and J)*** Incidence of study treatment related DLTs at Cycle 1 (Day 1 to Day 28). DLT will be defined as the occurrence of any of the following treatment-emergent adverse events (TEAEs) related to the study therapy using NCI-CTCAE (v4.03): • Any Grade ≥3 non-hematological toxicity, **except**: - Grade 3 nausea and vomiting resolving to Grade ≤1 within 48 hours, with or without adequate antiemetic treatment (all study arms) - Grade 3 diarrhea, if controlled with adequate antidiarrheal therapy and lasting less than 48 hours (all study arms) - Grade 3 hyperglycemia resolving to Grade ≤1 within 48 hours, with or without adequate treatment (Arm #4 Part H only) • Any Grade ≥3 hematological toxicity in all study arms, **except**: - Grade 3 anemia - Grade 4 neutropenia <7 days - Grade 3 neutropenia without fever or infection* - Grade 3 thrombocytopenia without bleeding. • Any elevated total serum bilirubin >2 x ULN in all study arms, except Part F • In addition, in Arm#3 (Parts F) only: - Grade 3 hyperglycemia (confirmed with a repeat FPG within 24 hours) not resolving to Grade ≤2 within 7 days after initiation of oral antidiabetic treatment, provided hyperglycemia did not lead to diabetic keto-acidosis, hospitalization for intravenous insulin infusion, or non-ketonic coma - Grade 2 hyperglycemia (confirmed with a repeat FPG within 24 hours) not resolving to Grade ≤1 within 21 consecutive days (after initiation of oral antidiabetic treatment) - Grade 2 ALT increase in conjunction with total blood bilirubin Grade ≥2 of any duration in the absence of liver metastases. - Grade ≥3 ALT and/or AST increase for more than 4 consecutive days - Grade 3 Rash and Maculopapular Rash not resolving to Grade ≤1 within 7 days, with or without adequate treatment (including systemic steroid use as per protocol) • Any toxicity related to study treatment, resulting in omission of the study treatment for 7 days or more during Cycle 1, or in Cycle 2 delay of more than 2 weeks in Parts C. • A TEAE that in the opinion of the Study Committee is possibly or probably study treatment-related and is of potential clinical significance such that further dose escalation would expose patients to unacceptable risk. These TEAEs will be considered as study treatment-related in the absence of evidence to the contrary and if not related to disease progression. If multiple toxicities are seen, the presence of DLTs will be based on the most severe experienced toxicity. At the end of Cycle 1, each patient must be assessed by the Investigator as to whether or not the patient experienced DLTs, and this information must be recorded within the appropriate screen of the electronic case report forms

	(eCRFs) and an electronic DLT notification (either DLT or not) will be sent to the Sponsor. Patients could continue the treatment after resolution (≤ Grade 1) of the adverse event (AE) or to their baseline status. Patients need to complete at least 75% of the intended doses at Cycle 1 to be evaluable, and in Part A only, should also have ^{18}F-FES-PET scans evaluable at baseline and between Day 11 and Day 15 to be evaluable for DLTs (see Section 13.8). The non-evaluable for DLT patients will be replaced, and additional patients could be treated if testing of other amcenestrant doses alone or with the current or other dose of palbociclib/alpelisib/everolimus/abemaciclib are needed upon agreement with the Study Committee. * G-CSF may be used to treat patients who have developed dose-limiting neutropenia, as per institutional guidelines (for Arm#3, alpelisib should be discontinued as per dose modification recommendations). ***Arm #1 Part B*** ORR: antitumor activity as documented by tumor response (CR or PR) defined by RECIST v1.1 determined by Independent Central Review (ICR). **Arms #2, #3, #4, and #5 (*Parts D, G, I, and K)*** Safety and tolerability: type, frequency, severity, relationship to study therapy and seriousness of adverse events (AE) or laboratory abnormalities according to NCI-CTCAE v4.03. **Of note:** the specific AESIs are ALT ≥ Grade 3 and photosensitivity. **Secondary endpoints** • Overall safety profile of amcenestrant, and characterization in terms of the type, frequency, severity, and relationship to study therapy of any AEs or abnormalities of physical findings, laboratory tests, or electrocardiograms (ECGs); drug discontinuation/omission/reduction and cycle delay due to AEs; or serious adverse events (SAEs) in all treatment arms. • ORR as per RECIST v1.1 (Parts A, B, C, D, F, G, H, I, J and K) assessed by investigators/local radiologists. • ORR and CBR in patients based on their ESR1 status (mutated or wild type) analyzed by multiplex droplet digital polymerase chain reaction (ddPCR) after extraction of plasma circulating DNA in Arms #1, #2, #3, #4, and #5 (all study parts). ORR assessed by investigators/local radiologists, and for Part B also by ICR. • Clinical benefit (CR+PR+SD ≥24 weeks) as per RECIST v1.1 assessed by investigators/local radiologists (Part A, B, C, D, F, G, H, I, J and K) and in Part B also determined by ICR • Duration of response assessed by investigators/local radiologists (in all treatment arms) and in Part B also determined by ICR • PFS in all treatment arms defined as the time interval from the date of the first IMP intake to the date of the first tumor progression assessed by investigators/local radiologists (and by IRC in Part B) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1), or death (due to any cause), whichever comes first • Time to first tumor response (CR or PR) in Arms #1, #2, #3, #4, and #5 (in all study parts) will be defined as the time interval from the date of

	first administration of the study treatment to the date of the first occurrence of CR or PR, assessed by investigators/local radiologists and in Part B also determined by ICR. • To correlate the changes observed in ^{18}F-FES-PET scan with the changes in glucose metabolism seen on FDG PET/CT in Part A BID • PK parameters for amcenestrant during Cycle 1: - After a single dose (on Day 1 Part A fasted state, B (fast or fed), C, D,H, I, J and K and Day 3 Part A (fed state)): at least t_{lag}, t_{max}, C_{max}, $AUC_{0-24,}$ or AUC_{0-12} and if possible for Part A Day 1, AUC, $t_{1/2z}$ and CL/F - After repeated administration (all treatment arms: fasting in Part A, fasting or fed in Part B, fed in Part C, D, F, G, H, I, J, and K) at least t_{max}, C_{max}, AUC_{0-24} or AUC_{0-12}. - C_{trough} (T=0 h ie, before daily administration) will be also obtained over Cycle 1. • Urine excretion of amcenestrant will be estimated during the monotherapy expansion phase (Part B). • PK parameters of palbociclib (fed): after first dose (Day 1) and after repeated once daily administrations (Day 21) during Cycle 1 (Parts C and D): at least t_{max}, C_{max}, AUC_{0-24}. • PK parameters of alpelisib (fed): after repeated administration alone or in combination with amcenestrant (Part F and G): at least t_{max}, C_{max}, AUC_{0-24} • PK parameters of everolimus (fed): after first dose (Day 1) and after repeated administration in combination with amcenestrant (Part H and I): at least t_{max}, C_{max}, AUC_{0-24} • PK parameters of abemaciclib and its metabolites M2, M18 and M20 (fed): after first dose (Day 1) and repeated administration in combination with amcenestrant (Part J and K): at least t_{max}, C_{max}, AUC_{0-12} • Potential for CYP3A enzyme induction and inhibition by amcenestrant: plasma 4β-hydroxy/total cholesterol concentration ratios on Day 22 versus Day 1 (Part B) or Cycle 2 Day 1 versus Day 1 Cycle 1 (Part A, Part J, Part K), or Cycle 2 Day 28 versus Day 1 Cycle 1 (Part J, Part K). • Inhibition of ER occupancy at ^{18}F-FES-PET imaging (signal extinction). All patients in Part A will have an ^{18}F-FES-PET/CT scan imaging performed at baseline and on treatment in addition to an FDG PET/CT which will be done in Part A BID at baseline and on treatment. For patients on a QD regimen, the second ^{18}FES PET scan will be performed after at least 8 continuous days of treatment (ie, between Day 11 and Day 15) and between 16 to 24 hours after the previous administration of the study drug, with a time window of 2 hours around 24 hour theoretical time. For patients on a BID regimen, the second scan for both ^{18}F-FES-PET and FDG PET/CT will be performed after at least 8 days of continuous treatment (ie, between Day 11 and Day 15 post first study treatment dose) and between 7 to 12 hours after the previous administration of the drug. The signal extinction between baseline and on study treatment ^{18}F-FES-PET scans will constitute the PD readout of the ER engagement. • ^{18}F-FES-PET or FDG PET/CT imaging will be performed in Part A only and Part A BID respectively only.

	Exploratory endpoints • **ER degradation:** In all patients in Arm#1 (Part A), and, in Arm#1 (Part B), Arm#3 (Parts F, G), Arm#4 (Parts H, I) and Arm#5 (Parts J,K), in patients who consented to, the paired biopsies will be asked for whether as the most recent archived biopsy (within past 3 months prior to initiation of study treatment) or, preferably, the fresh tumor biopsy which will be performed at baseline and at the end of Cycle 2. A total of 9 FFPE slides (5 micron each for IHC analysis) and 3 FFPE slides (10-µm each for RNA analysis, if possible) will be collected for each biopsy. The presence of ER will be determined by central IHC and the ER results at baseline and on treatment will be compared to assess ER degradation. • **ESR1 mutation status**: Twelve independent mutations of ESR1 gene will be determined in all patients at baseline and at end of Cycle 2 (Day 15 to Day 28) by digital droplet (ddPCR) PCR from plasma extracted cfDNA. For Arm#3 (Parts F, G), Arm#4 (Parts H, I) Arm#5 (Parts J, K), ESR1 mutation status will only be determined by broad mutational profile NGS and not limited to C2 on treatment evaluation. - The clinical responses will also be assessed in the ESR1 wild type and the ESR1 mutated population separately in Arm#1 (Part B). For Arm#3 (Parts F, G),Arm#4 (Parts H, I), Arm#5 (Parts J, K), CfDNA for ESR1 gene mutation status (by ddPCR) will not be collected but instead, the information of the ESR1 gene mutation status will be retrieved only from the CfDNA collected for mutational profile (NGS, multi-gene panel). • **Broad Mutational profile (NGS):** In all patients, plasma will be collected during the screening process and at the EOT and cfDNA will be extracted. For Arms #3 (Parts F, G), Arm #4 (Parts H, I), and Arm#5 (Parts J, K), additional plasma samples for cfDNA analysis by NGS will be collected at end of Cycle 2 and Cycle 4 (at tumor assessment). The mutation status of a limited number of cancer genes (including, but not limited to ESR1, *PIK3CA*) will be determined by the Next Generation Sequencing (NGS) and the potential link between specific mutation and clinical outcomes will be investigated to understand intrinsic or acquired resistance to the amcenestrant treatment. Germline mutations in saliva will be used as reference. • To evaluate PK/PD relationships of amcenestrant with ER occupancy, PD and/or efficacy endpoints and/or other breast cancer biomarkers such as Ki67, Bcl-2 and PgR. • To evaluate FDG SUV uptake before and during treatment with amcenestrant (Part A BID). • To correlate the changes observed in ^{18}F-FES-PET scan with the changes in glucose metabolism seen on FDG PET/CT in Part A

STATISTICAL CONSIDERATIONS	**Sample size justification** It is anticipated that up to approximately 251 patients will be enrolled into the study. The actual sample size will vary depending on DLTs observed, number of dose levels actually explored and the other potential schedules to be tested. According to different simulated scenarios, it is anticipated that approximately 25 DLT-evaluable patients will enter into the monotherapy dose escalation phase (Part A) of the study in QD regimen and 12 DLT-evaluable patients may enter the monotherapy dose escalation phase (**Part A**) in BID regimen. For Arm #1 **Part B**, it is anticipated that approximately 78 patients will enter into the dose expansion cohort of the study. For Arm #2 **Part C**, it is anticipated that approximately 12 DLT-evaluable patients will be required to establish the MTD and preliminary RD of SAR43859 when administered in combination with palbociclib. Additionally, a BID regimen could be explored in Part C. For Arm #2 **Part D**, it is anticipated that approximately 28 patients will be treated in an expansion phase at the selected RD (as per Study Committee recommendation) of amcenestrant with palbociclib in order to further assess the safety, tolerability and PK profiles of each RD and to explore preliminary antitumoral activity. For Arm #3 **Part F**, it is anticipated that approximately up to 6 DLT-evaluable patients will be required to establish RD of amcenestrant when administered in combination with alpelisib. For Arm #3 **Part G**, it is anticipated that approximately 34 patients will be treated in the expansion phase at the amcenestrant confirmed RD from Part F with alpelisib as per Study Committee agreement in order to further assess: safety, tolerability, PK profile and preliminary anti-tumoral activity of the confirmed amcenestrant RD and alpelisib combination therapy. For Arm #4 **Part H**, it is anticipated that approximately up to 12 DLT-evaluable patients will be required to establish RD of amcenestrant when administered in combination with everolimus. For Arm #4 **Part I**, it is anticipated that approximately 12 patients will be treated in an expansion phase at the selected RD (as per Study Committee recommendation) of amcenestrant with everolimus. For Arm #5 **Part J**, it is anticipated that approximately to 12 DLT-evaluable patients will be required to establish RD of amcenestrant when administered in combination with abemaciclib. For Arm #5 **Part K**, it is anticipated that approximately 20 patients will be treated in an expansion phase at the selected RD (as per Study Committee recommendation) of amcenestrant with abemaciclib. **General statistical approach** ***Populations*** DLT-evaluable population in dose escalation phase and dose safety run-in phase includes all patients who have received a first complete cycle (28-day, oral administration), taking at least 75% of the intended dosing, unless the patient discontinued the study treatment before Cycle 1 completion for a DLT, and in Part A, have an evaluable ^{18}F-FES-PET scans at baseline and between Day 11 and Day 15 of the first cycle. Any patient who develops a DLT in Part A despite the absence of evaluable ^{18}F-FES-PET scan will be included in the DLT population. A patient not evaluable who will discontinue the study treatment before the end of Cycle 1 for any reason other than DLT will be replaced.

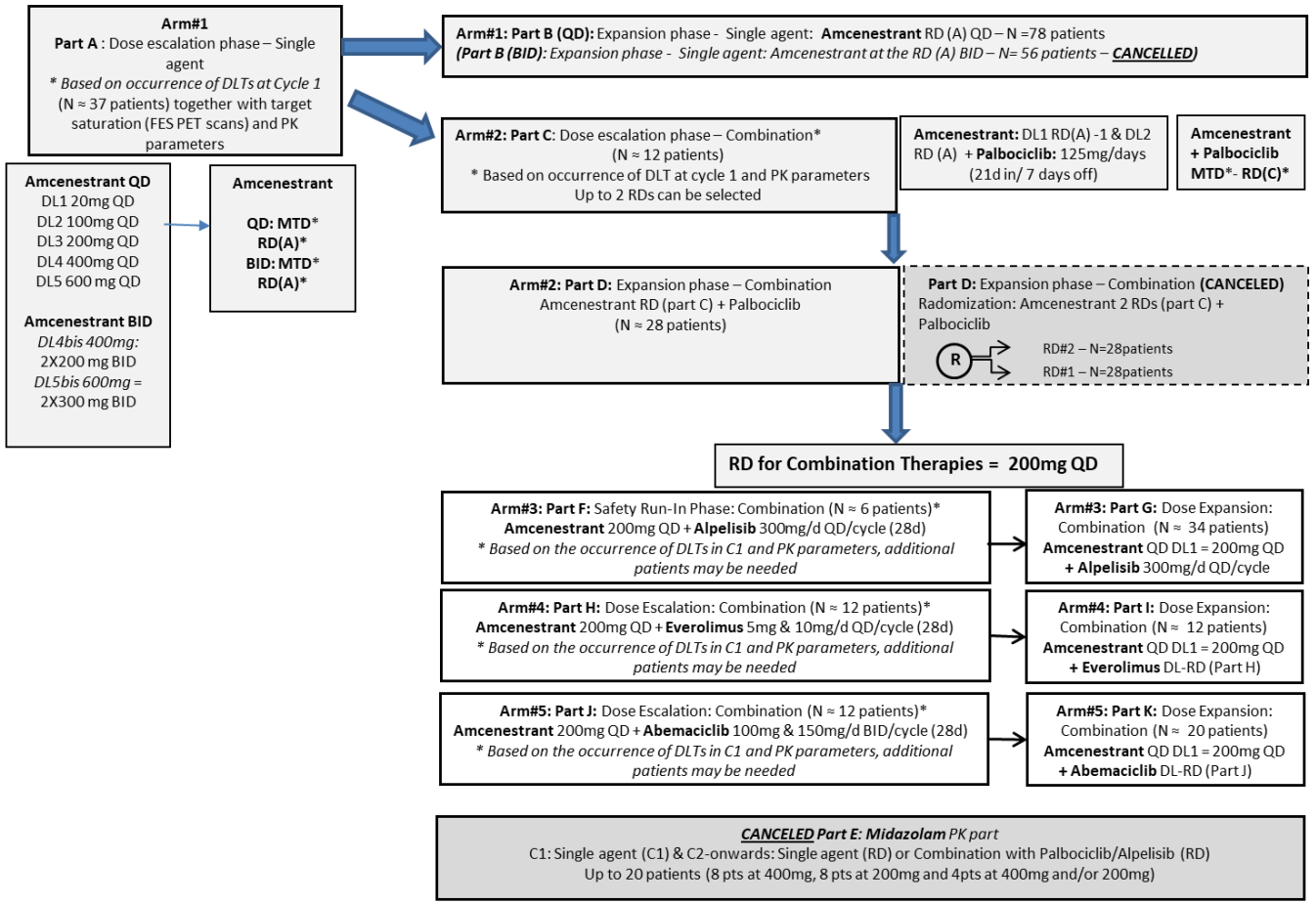
	Safety population includes all patients exposed to at least one dose of the study treatment. Response evaluable patients are defined as treated patients with measurable disease at study entry who had at least one postbaseline evaluable tumor assessment. Patients with an early progression as per RECIST v1.1 or who died from disease progression will be evaluable for response. PK evaluation will be performed on all patients without any major deviations related to study treatment administration (eg, early vomiting just after drug administration), and for whom any PK parameters are available. ***Arm #1 Part A (Dose Escalation Monotherapy)*** Study treatment-related DLTs occurring during Cycle 1 will be assessed and analyzed on the DLT-evaluable population. In addition, AEs meeting DLT criteria occurring in any additional cycle will be assessed and analyzed on the safety population. Safety and PK data will be descriptively summarized for each dose level on the safety population. Treatment emergent adverse events (TEAEs) will be analyzed according to current version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Laboratory abnormalities will be analyzed according to the NCI-CTCAE v.4.03. Type, frequency, seriousness, severity and relatedness of study treatment TEAEs will be analyzed on the safety population for each dose level. Dose proportionality will be assessed on pooled data from Parts A and B, using a power model on C_{max}, and AUC_{0-24} on Day 1 and Day 22. Accumulation ratio (Day 22/Day 1) for C_{max} and AUC_{0-24} or AUC_{0-12} will be estimated with 90% confidence intervals (CI) using a linear fixed effects model on log transformed parameters. Within-subject and total standard deviations for log(C_{max}) and log(AUC_{0-24} or AUC_{0-12} will be estimated (Parts A and B). The food effect will be assessed by comparing AUC_{0-24} and C_{max} between Day 1/Cycle 1 and Day 3/Cycle 1 Part A. 4β-hydroxy/total cholesterol concentration ratio (Cycle2/Cycle1) will be estimated with 90% CI. Preliminary efficacy will be descriptively presented on activity/efficacy population. ***Arm #1 Part B (Dose Expansion Monotherapy)*** It is assumed that the response rate is 10% under the null hypothesis according to literature with fulvestrant monotherapy in this population. It is expected that amcenestrant would induce a response rate of 20%. Under these hypotheses, with a one-sided 5% significance level with a power of 80%, it is anticipated that 78 patients for efficacy will be entered into the dose expansion cohort of the study. An interim analysis of the response rate will be done after treatment of the first 45 response patients. It is expected to have at least 5 patients with response (CR or PR); other parameters are also to be taken into consideration such as the duration of response, the CBR (CR + PR + SD ≥24 weeks), the percentage of patients with SD and the duration of SD. If a BID regimen is tested in the expansion cohort, with a one-sided 10% significance level with a power of 80%, it is anticipated that 56 patients could be entered into the dose expansion cohort of the study. Similar analyses as for the escalation phase will be performed. Response rate and other clinical outcomes will also be presented according to ESR1 status (mutation or wild type) for interim and final analysis.

	4β-hydroxycholesterol concentration ratio (Day 22/Day 1) will be estimated with 90% CI. ***Arm #2 Part C (Dose Escalation, combination with palbociclib)*** Similar statistical considerations as for Part A will be applied for Part C regarding safety and efficacy. Accumulation ratio (Day 21/Day 1) for C_{max} and AUC_{0-24} will be estimated with 90% CI using a linear fixed effects model on log transformed parameters for amcenestrant and palbociclib. Interaction ratio of amcenestrant on C_{max} and AUC_{0-24} for effect of palbociclib on amcenestrant will be estimated. ***Arm #2 Part D (Dose Expansion, Combination with palbociclib)*** Similar analyses will be performed in the combination dose expansion phase as for the escalation phase (Part C). ***Arm #3 Part F (Safety Run-In Phase, with alpelisib)*** Similar statistical considerations as for Part A will be applied for Part F regarding safety and efficacy. Interaction ratio of amcenestrant on C_{max} and AUC_{0-24} for effect of alpelisib on amcenestrant will be estimated using comparison with amcenestrant exposure in Part B (monotherapy). For alpelisib, the treatment effect of alpelisib in combination with amcenestrant versus alpelisib alone on log-transformed C_{max}, AUC_{0-24} will be analyzed with a linear mixed effects model for each amcenestrant dose level. Treatment (amcenestrant + alpelisib/alpelisib alone) differences and 90% CIs will be computed by first taking the mean logarithmic differences within the mixed model framework, and then converting them to ratios of geometric means using the anti-logarithmic transformation. ***Arm #3 Part G (dose expansion, combination with alpelisib***) Similar analyses will be performed in the combination dose expansion phase as in the safety run-in phase (Part F). ***Arm #4 Part H (Dose escalation, Combination with everolimus)*** Similar statistical considerations as for Part A will be applied for Part H regarding safety and efficacy. Accumulation ratio (Day 22/Day 1) for C_{max} and AUC_{0-24} will be estimated with 90% CI using a linear fixed effects model on log transformed parameters for amcenestrant and everolimus. ***Arm #4 Part I (Dose Expansion, Combination with everolimus***) Similar analyses will be performed in the combination dose expansion phase as in the dose escalation (Part H). ***Arm #5 Part J (Dose Escalation Phase, with abemaciclib)*** Similar statistical considerations as for Part A will be applied for Part J regarding safety and efficacy. Accumulation ratio (Day 22/Day 1) for C_{max} and AUC_{0-12} will be estimated with 90% CI using a linear fixed effects model on log transformed parameters for amcenestrant and abemaciclib. 4β-hydroxy/total cholesterol concentration ratio (Cycle2/Cycle1) will be estimated with 90% CI. ***Arm #5 Part K (Dose Expansion, Combination with abemaciclib***) Similar analyses will be performed in the combination dose expansion phase as in the dose escalation (Part J).

DURATION OF THE STUDY PERIOD (per patient)	**Duration of the entire study per patient** The duration of the study for an individual patient will include a period to assess eligibility (screening period) of up to 4 weeks (28 days), a treatment period of at least 1 cycle (28 days) of study treatment, and an EOT visit at least 22 to 30 days (or until the patient receives another anticancer therapy, whichever is earlier) following the last administration of study treatment. Study treatment may continue until precluded by unacceptable toxicity, disease progression, or upon patient's request. In Arms #2, #3, #4, and #5 (Parts C/D, F/G, H/I and J/K), palbociclib/alpelisib/everolimus/abemaciclib can be prematurely and permanently discontinued; in that case, amcenestrant can be continued as a single agent (monotherapy) until EOT criterion is met. The EOT visit in this case will be 30 days after the date of last amcenestrant administration. Patients who discontinue the study treatment prior to documentation of PD will be followed every 2 months until disease progression or initiation of further anti-cancer therapy, or cut-off date (COD), whichever comes first. Treatment may stop at any time if the study is terminated by the Sponsor. ***Duration of the entire study*** The expected enrolment period is approximately 60 months. There will be several cut off dates (COD) for this study: 1. In each study Arm dose escalation (Parts A, C, F, H and J), the first COD will be done at the end of the first cycle of the last patient treated in the given cohort study part in order to have at least the first cycle evaluable for all patients for determination of the MTD and for the RD. 2. The COD for each study Arm (dose escalation and dose expansion combined), for primary analysis, will be at each study Arm's LPI +12mos, except for Arm#2, in which the COD will be at LPI+20 months 3. The final study COD will be performed when the last study Arm will have reached its COD 4. In addition, for all study parts, informal analyses could be performed on as needed basis during the study to support further development of the compound and regulatory requirements. After each study Arm COD, ongoing patients will receive study therapy until disease progression, occurrence of an unacceptable toxicities, whichever is earlier, and they will only be followed <u>for study treatment administration, SAEs, study treatment-related AEs and AEs leading to study treatment discontinuation.</u>

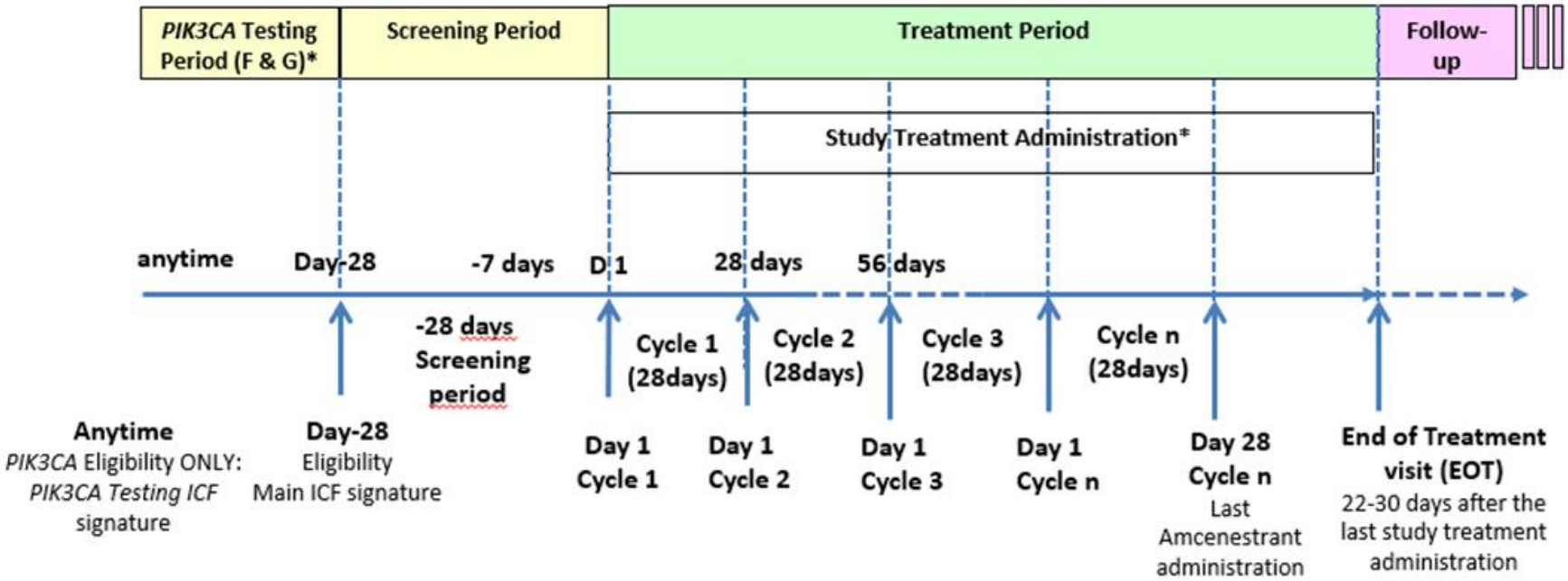
1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN - DOSING SCHEME



Abbreviations: DL= Dose Level, DLT=Dose Limiting Toxicity, MTD= Maximum Tolerated Dose, RD = Recommended Dose, PK=pharmacokinetics, PD=pharmacodynamics

1.2 GRAPHICAL STUDY DESIGN - STUDY SCHEDULING



- Study treatment Arm#1 Part A: Amcenestrant once daily or twice daily for 28 days in all cycles
- Study treatment Arm#1 Part B: Amcenestrant once daily for 28 days in all cycles
- Study treatments Arm#2 Parts C and D: Amcenestrant once daily, and palbociclib once daily for 21 days followed by 7 days off of therapy
- Study treatments Arm#3 Parts F and G: both, amcenestrant and alpelisib taken once daily for 28 days in all cycles (Cycle 1 only will start with alpelisib alone from Day 1 to Day 3 followed by amcenestrant from Day 4)
- Study treatment Arm#4 Parts H and I: Amcenestrant and everolimus once daily for 28 days in all cycles
- Study treatment Arm#5 Parts J and K: Amcenestrant once daily for 28 days and abemaciclib twice a day in all cycles

** PIK3CA Testing applicable ONLY to Parts F and G: to do at anytime, locally, on patients who have not had PIK3CA test confirmed/detected yet; and to do PRIOR to the main consenting and initiation of the screening procedures*

1.3 STUDY FLOWCHART

Evaluation[a]	Pre-Screening	Screening	Treatment Cycle 1					Subsequent cycles[d]					End-of-treatment (EOT)
		D-28 to D1	D1[b]	D3	D8 (±1)	D15 (±2)	D22[c] (±2)	D1[b] (±2)	D8 (±2)	D15 (±2)	D22 (±2)	D28 (±2)	D22-D30 (after last administration of study treatment)[bb]
Inclusion/exclusion criteria/informed consent		X											
Demographic and medical/disease history		X											
ECOG performance status/body weight/height[e]		X	X			X		X		X			X
Vital signs, physical examination/signs and symptoms[f]		X	X		X	X	X	X	X	X	X		X
Blood hematology[g]		X	X		X	X	X	X	X	X	X		X
Coagulation[h]		X	X			X		X		X			X
Blood chemistry[i]		X	X		X	X	X	X	X	X	X		X
12-lead electrocardiogram[j]		X	X					X					X
Urinalysis[k]		X	X			X		X		X			X
Amcenestrant administration[l]			Continuous once or twice daily										
Palbociclib administration once daily (Arm #2 Parts C and D)[m]			Day 1 to 21					Day 1 to 21					
Alpelisib administration once daily (Arm #3 Parts F and G)[dd]			Continuous once daily										
Everolimus administration once daily (Arm #4 Parts H and I)[gg]			Continuous once daily										

Evaluation[a]	Pre-Screening	Screening	Treatment Cycle 1					Subsequent cycles[d]					End-of-treatment (EOT)
		D-28 to D1	D1[b]	D3	D8 (±1)	D15 (±2)	D22[c] (±2)	D1[b] (±2)	D8 (±2)	D15 (±2)	D22 (±2)	D28 (±2)	D22-D30 (after last administration of study treatment)[bb]
Abemaciclib administration twice daily (Arm #5 Parts J and K)[gg]			Continuous twice daily										
Hospitalization[n]			X				X	X					
^{18}F-FES-PET scan and FDG PET/CT (Part A Only)[o]		X				D11 to D15							
Adverse events assessment[p]		Continuous throughout study assessment											
Concomitant medications[q]		Continuous throughout study assessment											
Patient diary review				X	X	X	X	X	X	X	X	X	X
Tumor assessments													
RECIST v1.1, CT/MRI[r]		X										X	X
Pharmacokinetics/pharmacogenetics													
Amcenestrant PK assessment[s]			X	X[t]	X	X	X	X[u]				X[v]	
Palbociclib PK assessment[w]			X		X	X	X	X[u]					
Alpelisib PK assessment				X[cc]	X	X	X[cc]						
Everolimus PK assessment[hh]			X				X						
Abemaciclib PK assessment[ii]			X				X						
DMET genotyping[x]			X										

Evaluation[a]	Pre-Screening	Screening	Treatment Cycle 1					Subsequent cycles[d]					End-of-treatment (EOT)
		D-28 to D1	D1[b]	D3	D8 (±1)	D15 (±2)	D22[c] (±2)	D1[b] (±2)	D8 (±2)	D15 (±2)	D22 (±2)	D28 (±2)	D22-D30 (after last administration of study treatment)[bb]
Pharmacodynamics													
Tumor specimen/biopsy[y]		X										X	
ESR1 status in cfDNA (ddPCR, plasma)[z]			X									X	
Molecular profiling in cfDNA (NGS, plasma)[aa]		X										X[jj]	X
Germline DNA reference (saliva) [aa]			X										
PIK3CA Testing[ee]	X												
Estradiol (Serum) [ff]			X (except for Part A, C, H, and J)									X (except for Part A, C, H, and J)	

a Evaluation: Assessments should be performed when possible prior to administration of study treatment unless otherwise indicated. Every effort should be made to keep the schedule of assessments on time for each patient. All visits should be performed on the day specified, unless otherwise noted. Additional safety tests (eg, electrocardiogram) can be performed whenever clinically indicated. All the tests or procedures on Day 1 should be done at predose time unless otherwise stated.

b **Part A:** Cycle 1 Day 1 refers to the day the patient receives the initial dose of study treatment which will be a single administration of amcenestrant, there will be no drug administration on Day 2; from Day 3, it will be once/twice daily administration (QD/BID) of amcenestrant in Part A.

In Arms #1, #2, #4, and #5 (Parts B, C, D, H, I, J and K), amcenestrant is given QD from Day 1 Cycle 1 and from Day 4 for Arm#3 (Part F, G). Before Cycle 1, repeated evaluation of body weight, signs and symptoms, physical examination, electrocardiogram, hematology, coagulation tests, blood chemistry and urinalysis should occur within 2 days before the study treatment administration if abnormal or to be performed more than 7 days before study treatment administration. The Day 8-time window at Cycle 1 is ±1 day. The Day 15 and Day 22 time windows at Cycle 1 are ±2 days (see footnote [c] for the timing of this visit in Parts C and D). For subsequent cycles, Day 1, Day 8, Day 15 and Day 22 visit time windows are ±2 days. In the combination therapies, a visit/cycle will be delayed if start date of the current cycle minus start date of previous cycle >31 days (28 +3 days). In case when all screening procedures have been completed and the patient is confirmed to be eligible, the Screening visit, and Cycle 1 Day 1 could be performed on the same day.

c In Parts C, D this visit must take place on Day 21 (instead of D22) to coincide with the last day of dosing of palbociclib.

d Weekly visits during Cycle 1 and 2; from Cycle 3 to Cycle 6 (inclusive), visits to be every 2 weeks, in subsequent cycles (ie, from Cycle 7 and onwards), visits to be once a month. Day 8 and Day 22 visits and associated exams are applicable only for Cycles 1 and 2. Day 28 of the previous cycle may overlap with Day 1 of the next cycle if all procedures planned for the new cycle are completed before amcenestrant administration.

e Height: will be assessed at baseline. ECOG performance status and weight: will be assessed at baseline, on Day 1, Day 15 Cycle 1 to Cycle 6 (inclusive), Day 1 from Cycle 7 and onwards, and at the EOT.

f Vital signs will be assessed at baseline, on Day 1, Day 8, Day 15, and Day 22 from Cycle 1 to Cycle 6 (inclusive), Day 1 from Cycle 7 and onwards, and at EOT; it will include body temperature, blood pressure, heart rate and respiratory rate which are to be measured after sitting for10-minutes in a supine position. Only clinically relevant signs and symptoms will be reported as AEs in the eCRF.

g **Hematology:** Hemoglobin, white blood cell count with differential, platelet counts. If Grade 3 neutropenia, repeat complete blood count monitoring it within 1 week (or as per Investigators' judgement). If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC ≥0.5 x 10^9/L and at least weekly thereafter until ANC ≥1.0 x 10^9/L. Blood count will be performed weekly at Cycle 1 and 2, then every 2 weeks (Days 1 and 15) from Cycle 3 to 6, and every 4 weeks (Day 1) in subsequent cycles from cycle 7. For Arm#5 (Parts J and K): Monitor white blood count with differential prior to start of abemaciclib treatment (screening period), every 2 weeks for the first 2 cycles (ie, C1D1 & D15 and C2D1 & D15), then every 4 weeks for the next 2 cycles (ie, C3D1 & C4D1), and afterwards as clinically indicated.

h **Coagulation:** prothrombin time and INR. **For Arm #3, Parts F and G,** to add: activated Partial Thromboplastin Time (aPTT). It will be assessed at baseline, on Day 1 and Day 15 from Cycle 1 to Cycle 6 (inclusive), Day 1 from Cycle 7 and onwards, and at EOT.

i **Blood chemistry:** Liver function tests (LFTs): aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, conjugated bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT). Serum Albumin. Electrolytes: sodium, potassium, chloride, magnesium, calcium, phosphate, bicarbonate or BUN and creatinine. Additional tests will be performed when clinically appropriate. In case of Grade 3 or higher liver function abnormal tests; additional tests will be done every 2 to 3 days until recovery to baseline value. Blood chemistry will be performed in any study arms weekly at Cycles 1 and 2, then every 2 weeks (Days 1 and 15) from Cycle 3 to 6, and every 4 weeks (Day 1) in subsequent cycles from cycle 7.

In Arm #3 and #4 (Part F, G, H, and I) only: *Fasting Serum Glucose* sample for safety assessment will be collected after 8-12 hours of an overnight fasting, prior to the light breakfast at the following timepoints: baseline (approximately 2 weeks before C1 Day 1), in C1 (Day 8 and Day 15), C2 (Day 1, Day 15 and Day 28), and monthly thereafter (ie, on Day 1 in subsequent cycles), and EOT. Additional measurements may be performed as clinically indicated.

***Hemoglobin A1C (HbA1C)* will be assessed for safety after 8-12 hours of an overnight fasting, pre-dose prior to the light breakfast, at the following timepoints: baseline (approximately 2 weeks before C1 Day 1), Cycle 1 and Cycle 2 Day 1, Day 1 of every 3rd cycle (ie, C5D1, C8D1 etc.), EOT and when clinically indicated.**

In Arm #4 (Parts H and I): lipid panel, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides and total cholesterol

j **12-lead electrocardiogram:** at baseline, start of each cycle from Cycle 2 and EOT; to be repeated as clinically indicated.

k **Urinalysis:** Dipstick or qualitative analysis for pH, glucose, ketones, blood, protein and leucocytes, will be assessed at baseline and on Day 1 and 15 of each cycle, at EOT and if clinically relevant. Patients with 3+ or greater urine protein dipstick reading should undergo further assessment with a 24-hour urine collection for determination of proteinuria.

l In **Arm #1 dose escalation Part A**, amcenestrant will be administered QD/BID within a 28-day cycle. In Part A, QD regimen, in Cycle 1, one dose is administered on Day 1 in fasted condition, none on Day◦2 and repeated once daily in fasted condition from Day◦3. On Day◦3 only, the dose is administered in fed condition. In **Part B**, amcenestrant will be administered in fasting or fed conditions. In **Part C and D**, amcenestrant and palbociclib will be taken together, with food, 5 minutes apart, regardless of the order of intake.Amcenestrant will be dispensed every 2 weeks.

In Arm #5 **Parts F and G**, amcenestrant will be administered daily from Cycle 1 Day 4 at assigned dose levels, within a 28-day cycle together with alpelisib in fed condition, and at approximately the same time each day (±3 hours). In case of the alpelisib premature discontinuation, amcenestrant treatment can continue as a single therapy (monotherapy), and it must be taken with food, in cycles of the 28-days duration. The days of PK assessment (ie, on C1D3 and C1D22) the drugs will have to be taken together after a standard breakfast.

In Arm #4 and #5 (**Parts H and I / J and K),** amcenestrant and everolimus / abemaciclib will be taken together at approximately the same time each day (±3 hours), with food, administered daily from Cycle 1 Day 1 at assigned dose levels, within a 28-day cycle. The days of PK assessment (*ie,* C1D1 and C1D22) the combinations amcenestrant with everolimus for Parts H, I and amcenestrant with abemaciclib for Parts J, K will have to be taken together after a standard breakfast.

m In **Arm #2 (Parts C and D)** (starting from Cycle 2 Day 1), palbociclib will be systematically administered during the meal for 21 consecutive days followed by 7 days off treatment within a 28-day cycle. Palbociclib will be dispensed every 4 weeks.

n **Hospitalization**: if necessary, one day of hospitalization can be envisioned assuming that all planned exams could be performed within that period. Hospitalization would be recommended mainly on Day 22 due to the PK sampling schedule, and if needed, in Cycle 2 Day 1.

o **^{18}F-FES-PET scan (Part A QD and BID) and FDG PET/CT (Part A BID only)**: will be performed in all patients of Part A at baseline (within 3 days or more prior to Day 1) and between Day 11 and Day 15 in Cycle 1.

p **Adverse event assessment:** The period of observation for collection of AEs extends from informed consent signed, until at least 30 days after the last administration of study treatment. Ongoing SAEs and ongoing related AEs should be followed beyond EOT until resolution or stabilization.

q **Concomitant medications:** the period of collection of concomitant medications extends from the date of the informed consent signature until EOT and post EOT if associated with ongoing SAE or ongoing related AEs.

r **Tumor assessment:** chest, abdomen, and pelvis CT scan or MRI scan and any other exams as clinically indicated to be performed to assess disease status at baseline. The same body parts' (ie, chest abdomen, and pelvis) CT or MRI scan (whichever was used at baseline) should be performed every 8 weeks from C1D1 with flexibility of +/- 7 days, approximately corresponding to the even-numbered cycles (eg, Cycles 2, 4, 6, 8, etc) or when clinically indicated during treatment, whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or CR, and at the end of study treatment (RECIST v1.1 for solid tumors see Appendix C). Tumor assessment should not be repeated at EOT if performed at immediate prior cycle. Date of disease progression or date of first further anticancer therapy (whichever is earlier) will be collected in follow up for patients who discontinue the study treatment prior to documentation of disease progression. Follow up will be performed approximately every 2 months. Imaging should be available for central review for Part B.

s **PK amcenestrant**: see detailed PK/PD flowchart.

t PK samples collected on Day 3 only in the QD regimen of Part A (not to be collected for the BID sampling regimen).

u Pre-dose PK sampling Cycle 2 only.

v Only for Parts B, D and G sparse PK sampling (see Section 1.4.1.2.2, Section 1.4.2.1.2, and Section 1.4.3.1.2)

w **PK palbociclib**: see detailed PK/PD flowchart (Section 1.4.2).

x **DMET genotyping**: for patients who agreed to this in the informed consent form, one blood sample prior to study treatment initiation will be dedicated for DMET genotyping.

y **Tumor sampling**: For all patients in Part A and for patients in Part B, Arm#3, #4 and #5 who consent to paired biopsies (before treatment and during treatment) and with tumor accessible: 1) preferably fresh biopsy or archived tumor tissues (within past 3 months prior to initiate of study treatment) will be collected and centrally analysed for IHC at Screening. 2) On-treatment biopsy should be performed at the end of Cycle 2 (between Day 15 and Day 28). (See detailed PK/PD flowchart).

z **ESR1 mutation by dd-PCR**: One blood sample will be collected and processed for cfDNA analyses of ESR1 mutation status by droplet digital PCR (all patients) at baseline and at the end of Cycle 2 (between Day 15 and Day 28). This does not apply to **Parts F, G**, H, I, J and K. ESR1 mutation status in Parts F,G,H,I,J and K will be provided by molecular profiling panel and not by ESR1 focused panel.

aa **Molecular profiling by NGS**: two blood samples (plasma) will be collected at screening and at the EOT to determine mutation profiles by next generation sequencing in cfDNA (all patients). Molecular profiling will be performed by NGS. For **Parts F, G**, H, I, J and K, cfDNA will be collected at screening, end of Cycle 2 and Cycle 4 (at the time of tumor assessment), as well as EOT/Progression. Saliva **germline mutation analysis:** Saliva will be collected at baseline to extract germline DNA which will be used as reference for tumor mutational analysis.

bb If further therapy is initiated before D22 after last IMP, investigator should contact the patient (either by phone call or visit) to obtain final collection of safety information (stabilization or recovery of TEAEs) within 30 days after last IMP intake or in follow up visit in case of ongoing SAE or related AE. Patients who discontinue the study treatment prior to documentation of PD will be followed every 2 months until disease progression or initiation of further anticancer therapy, or cut-off date dates (COD), whichever comes first (see Section 6.8.1).

cc PK alpelisib: see detailed PK/PD flowchart.

dd Alpelisib will be administered daily with food within 28-day cycles starting from Cycle 1 Day 1 for Part F and G

ee ***PIK3CA* Testing:** For Parts F and G only: Detected PIK3CA mutation(s) in solid biopsy or plasma is mandatory for patients' eligibility. This PIK3CA testing must be performed locally. For patients not having prior access to PIK3CA testing, but willing to have it performed, in order to be eligible (if mutation detected), will have to sign the Pre-screening PIK3CA Testing ICF before the main consenting and screening process begins. No fresh biopsy will be required from Sponsor for eligibility purposes. All PIK3CA reports regardless of the time of testing (recent/archival) are acceptable.

ff Estradiol: samples collected on C1D1 and C2D28 see detailed PK/PD flowchart.

gg Everolimus (Arm #4 Parts H, I) and abemaciclib (Arm #5 Parts J, K) will be administered with food during the study. On the days of PK assessment (ie, C1D1 and C1D22) where the combinations amcenestrant with everolimus for Parts H, I and amcenestrant with abemaciclib for Arm #5 Parts J and K will have to be taken together after a standard breakfast.

hh PK everolimus: see detailed PK/PD flow chart

ii PK abemaciclib: see detailed PK/PD flow chart

jj For Arms #3, 4, and 5, samples should be collected at the end of C2, end of C4, and at EOT (but not at the end of other cycles).

AE = adverse event; Blood Urea Nitrogen (BUN); aPTT = activated Partial Thromboplastin Time ; cfDNA = circulating free DNA; COD = cut-off dates, CR = complete response; CT = computerized tomography; D = day; DMET = drug metabolizing enzymes and transporters; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; ER = estrogen receptor; ESR1 = estrogen receptor 1; ^{18}F-FES-PET = $^{(18)}$F-fluoroestradiol-positron emission tomography; (^{18}FDG) = fluorodésoxyglucose (^{18}F); IHC = immunohistochemistry; INR = international normalized ratio; MRI = magnetic resonance imaging; NGS= next generation sequencing; PCR = polymerase chain reaction; PD = pharmacodynamics; PK = pharmacokinetics; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event.

1.4 PHARMACOKINETIC AND PHARMACODYNAMIC FLOW CHART

1.4.1 Arm #1

1.4.1.1 Part A

Cycle		**PART A Cycle 1**											
Day within cycle	**Day -3**	**Day 1**										**Day 2**	
Relative Nominal Time		**0 h**	**0.5 h**	**1 h**	**1.5 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**10 h**	**24 h**	**36 h**
Time window		**[-10 min, 0 h]**	**±5 min**	**±10 min**	**±15 min**	**±15 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±1 h**	**±1 h**	**±1 h**
Indicative clock time		08:00	08:30	09:00	09:30	10:00	11:00	12:00	14:00	16:00	18:00	08:00	20:00
Amcenestrant administration[a]													
Once/twice Daily		X											
Amcenestrant pharmacokinetics[j]													
Plasma		P00[b, k]	P01	P02	P03	P04	P05	P06	P07	P08	P09	P10	P11
Pharmacogenetics (DMET genotyping)													
DMET analysis		B00[b]											
Pharmacodynamics													
Plasma (cfDNA-ESR1 by dd-PCR)[c]		ER00											
^{18}F-FES-PET and FDG imaging[d]	X												
Plasma (cfDNA-NGS mutational profiling)[e]		CF00											
Saliva (germline DNA)[e]		SA00											
Tumor specimen[i]	A0												
Tumor biopsy[i]	S0												

Cycle	**PART A Cycle 1**												
Day within cycle	**Day 3/4**											**D8**	**Between Day 11 and Day 15**
Relative Nominal Time	**0 h**	**0.5 h**	**1 h**	**1.5 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**10 h**	**24 h**	**0 h**	**0 h**
Time window	**[-10 min, 0 h]**	**±5 min**	**±10 min**	**±15 min**	**±15 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±1 h**	**±1 h**	**[-10 min, 0 h]**	
Indicative clock time	08:00	08:30	09:00	09:30	10:00	11:00	12:00	14:00	16:00	18:00	08:00	08:00	08:00
Amcenestrant administration[a]													
Once/twice daily	X[f]										X	X	X[h]
Amcenestrant pharmacokinetics[j]													
Plasma	P12[b]	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22[b]	P23[b]	P24[g]
Pharmacodynamics													
^{18}F-FES-PET and FDG imaging[d]													X

Cycle	PART A Cycle 1											Cycle 2		EOT
Day within cycle	**Day 22/23**											**Day 1**	**Day 28**	**Day 22-30**
Relative Nominal Time	**0 h**	**0.5 h**	**1 h**	**1.5 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**10 h**	**24 h**	**0 h**		
Time window	**[-10 min, 0 h]**	**±5 min**	**±10 min**	**±15 min**	**±15 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±1 h**	**±1 h**	**[-10 min, 0 h]**		
Indicative clock time	08:00	08:30	09:00	09:30	10:00	11:00	12:00	14:00	16:00	18:00	08:00	08:00		
Amcenestrant administration[a]														
Once/twice daily	X										X	X		
Amcenestrant pharmacokinetics[j]														
Plasma	P25[b]	P26	P27	P28	P29	P30	P31	P32	P33	P34	P35[b]	P36[b, k]		
Pharmacodynamics														
Plasma (cfDNA-ESR1 by dd-PCR)[c]													ER001	
Plasma (cfDNA-NGS mutational profiling)[e]														CF01
Saliva (germline DNA)[e]														
Tumor biopsy[i]													T1	

a A single administration of amcenestrant on Day 1, no administration on Day 2 and once or twice daily administration of amcenestrant from Day 3. For the QD dosing regimen, all patients will receive amcenestrant doses in fasting condition in the morning (ie, the drug will be taken after an overnight fast of at least 10 hours and at least 3h before breakfast on D1 and D22 and 2 hours the other days). On Day 3, a full PK evaluation will be done in fed state for all patients, the drug will be taken after a standard meal. For the BID dosing regimen, pilot food effect will not be conducted on Day 3. Amcenestrant will be taken independent of the food conditions at approximately the same time each day.

b *Sample collected just before amcenestrant administration.*

c Plasma will be collected at baseline and at end of Cycle 2 (between Day 15 and Day 28) to determine the ESR1 mutation status in cfDNA by droplet digital PCR.

d A first full body PET/CT scan imaging, after intravenous injection of ^{18}F-radiolabelled estradiol to be done 3 days or more before the start of treatment and a second scan to be at least 8 days after once a day of continuous treatment (ie, between Day 11 and Day 15). For QD regimen, the ^{18}F-FES-PET scan should be completed between 16 to 24 hours after the previous administration of the drug, with a time window of 2 hours around the 24 hour theoretical time. For BID regimen, the ^{18}F-FES-PET scan should be completed between 7 to 12 hours after the previous administration of the drug. Patients should be instructed to take the previous study treatment dose at the appropriate time in line with availability of the PET/CT scan at sites. If limited response is observed at that time, an earlier ^{18}F-FES-PET time window may be considered. Additionally, an FDG will also be performed for Part A BID patients only.

e Plasma will be collected in all patients to monitor mutational profiling of the tumor by NGS in cfDNA at baseline (CF00) and at the EOT (CF01). Saliva germline mutation analysis: Saliva will be collected at baseline to extract germline DNA which will be used as reference for tumor mutational analysis.

f **For QD regimen only**: The food effect evaluation will be done on Day 3: all patients will receive amcenestrant doses in fed state in the morning (ie, after an overnight fast of at least 10 hours, a standard meal will be taken within 30 minutes and amcenestrant will be administered within 5 minutes after meal completion).

g PK sample taken the day of the ^{18}F-FES-PET scan and FDG PET/CT just before ^{18}F-radiolabelled estradiol administration.

h The day of ^{18}F-FES-PET scan and FDG PET/CT, the patient will receive the amcenestrant dose just after imaging procedures.

i When patients consent for paired biopsies, a tumor sample is required at baseline: either the most recent FFPE tumor specimen (within past 3 months prior to initiation of study treatment, A0) should be provided or preferably a fresh biopsy (S0) can be performed but is not mandatory and collection of an on-treatment biopsy (T1) should be done in at least 10 patients at the recommended dose to assess centrally at least ER degradation by IHC. Day of collection of biopsy under treatment should be at the end of Cycle 2 (between D15 to D28). Time of sampling in relation to dose administration should be noted.

j For Part A BID dosing regimen, a twice a day drug administration will be planned over the 28-day cycle. The PK samples planned on Day 3, Day 4 and the 24 hour sample on Day 22/23 are not necessary.

k Plasma 4β-OH and total cholesterol assessment to be done.

Note: For the comfort of patients, some PK samplings may be deleted during the course of the study if they are no longer deemed necessary by the Sanofi PK team.

CfDNA = circulating free DNA; CT = computerized tomography; DMET = drug metabolizing enzymes and transporters; EOT = end of treatment; ESR1 = estrogen receptor 1; ^{18}F-FES-PET = (18) F-fluoroestradiol-positron emission tomography; NGS= Next Generation Sequencing; PCR = polymerase chain reaction; PK = pharmacokinetics.

1.4.1.2 Part B

At least 12 patients will be sampled according to following PK/PD flow chart in Section 1 (full PK sampling). For the remaining patients of the cohort, a sparse sampling approach for PK with 3 to 4 time points on Day 1, and 3 to 4 time points on Day 22 is presented in Section 1.4.1.2.2.

1.4.1.2.1 Part B Full PK Sampling

Cycle		**PART B Cycle 1**											
Day within cycle		**Day 1/2**										**Day 8**	**Day 15**
Relative Nominal Time		**0 h**	**0.5 h**	**1 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**10 h**	**24 h**	**0 h**	**0 h**
Time window		**[-10 min, 0 h]**	**±5 min**	**±10 min**	**±15 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±1 h**	**±1 h**	**[-10 min, 0 h]**	**[-10 min, 0 h]**
Indicative clock time		08:00	08:30	09:00	10:00	11:00	12:00	14:00	16:00	18:00	08:00	08:00	08:00
Amcenestrant administration[a]													
Once daily		X									X	X	X
Amcenestrant pharmacokinetics													
Plasma[b]		P00[c, d]	P01	P02	P04	P05	P06	P07	P08	P09	P10[c]	P11[c]	P12[c]
Urine													
Pharmacogenetics (DMET genotyping)													
DMET analysis		B00[c]											
Pharmacodynamics													
Tumor specimen[e]	A0												-
Tumor biopsy[e]	S0												
Plasma (cfDNA – NGS mutational profiling)[f]		CF00											
Saliva (germline DNA)[g]		SA00											
Plasma (cfDNA - ESR1 by dd-PCR)[h]		ER00											

Cycle	PART B Cycle 1										Cycle 2		EOT
Day within cycle	**Day 22/23**										**Day 1**	**Day 28**	**Day 22-30**
Relative Nominal Time	**0 h**	**0.5 h**	**1 h**										
Time window	**[-10 min, 0 h]**	**±5 min**	**±10 min**	**±15 min**									
Indicative clock time	08:00	08:30	09:00	10:00	11:00	12:00	14:00	16:00	18:00	08:00	08:00		
Amcenestrant administration[a]													
Once daily	X									X	X		
Amcenestrant pharmacokinetics													
Plasma[b]	P13[c, d]	P14	P15	P17	P18	P19	P20	P21	P22	P23[c]	P24[c]		
Urine	←	------	----	-------	-------	U00	------	-------	------	→			
Pharmacodynamics													
Plasma (cfDNA - ESR1 by dd-PCR)[h]												ER001	
Tumor biopsy[e]												T1	
Plasma (cfDNA-mutational profiling)[f]													CF01
Saliva (germline DNA)[g]													

a On the basis of preliminary PK information from the pilot food effect in Part A and safety information, amcenestrant can be taken with or without food.

b Circulating amcenestrant metabolites will be explored.

c Sample collected just before amcenestrant administration.

d Amcenestrant plasma samples will be used also for 4β-hydroxycholesterol measurement.

e When patients consent for paired biopsies, a tumor sample is required at baseline: either the most recent FFPE tumor specimen (within past 3 months prior to initiation of study treatment, A0) should be provided or preferably a fresh biopsy (S0) can be performed but is not mandatory and collection of an on-treatment biopsy (T1) should be done in at least 10 patients at the recommended dose to assess centrally at least ER degradation by IHC. Day of collection of biopsy under treatment should be at the end of Cycle 2 (between D15 to D28). Time of sampling in relation to dose administration should be noted.

f Plasma will be collected in all patients to monitor mutational profiling of the tumor in cfDNA by NGS at baseline (CF00) and at the EOT (CF01).

g Saliva **germline mutation analysis:** Saliva will be collected at baseline (SA00) to extract germline DNA which will be used as a reference to determine tumor somatic mutations in CfDNA.

h Plasma (ER00) will be collected at baseline and (ER001) at end of Cycle 2 (between D15 to D28) to determine the ESR1 mutation status in cfDNA by droplet digital PCR.

Note: For the comfort of patients, some PK samplings may be omitted during the course of the study if they are no longer deemed necessary by the Sanofi PK team

CfDNA = circulating free DNA; DMET = drug metabolizing enzymes and transporters; EOT = end of treatment; ESR1 = estrogen receptor 1; FFPE = formalin-fixed paraffin-embedded; PCR = polymerase chain reaction; PK = pharmacokinetics.

1.4.1.2.2 Part B Sparse PK sampling

Cycle		**PART B Cycle 1**										**Cycle 2**		**EOT**
Day within cycle		**Day 1**		**Day 8**		**Day 15**		**Day 22**				**Day 1**	**Day 28**	**Day 22-30**
Time window			**[1 h - 2 h]**	**[3 h - 5 h]**	**[7 h - 9 h]**	**[-10 min, 0 h]**	**[-10 min, 0 h]**	**[-10 min, 0 h]**	**[1 h- 2 h]**	**[3 h - 5 h]**	**[7 h - 9 h]**	**[-10 min, 0 h]**		
Indicative clock time		08:00	[09:00 - 10:00]	[11:00 - 13:00]	[15:00 - 17:00]	08:00	08:00	08:00	[09:00 - 10:00]	[11:00 - 13:00]	[15:00 - 17:00]	08:00		
Amcenestrant administration[a]														
Once or twice daily		X				X	X	X				X		
Amcenestrant pharmacokinetics														
Plasma			P00	P01	P02	P03[b]	P04[b]	P05[b]	P06	P07	P08	P09[b]	P10[g]	
Pharmacogenetics (DMET genotyping)														
DMET analysis		B00[b]												
Pharmacodynamics														
Tumor specimen[c]	A0													
Tumor biopsy[c]	S0							_	_	_	_	_	T01 ➔	
Plasma (cfDNA – NGS mutational profiling)[d]		CF00												CF01
Saliva (germline DNA)[e]		SA00												
Plasma (cfDNA - ESR1 by dd-PCR)[f]		ER00											ER001	
Serum (Estradiol)		ES00											ES01	

a On the basis of preliminary PK information from the pilot food effect in Part A and safety information, amcenestrant can be taken with or without food.

b Sample collected just before amcenestrant administration.

c When patients consent for paired biopsies, a tumor sample is required at baseline: either the most recent FFPE tumor specimen (within past 3 months prior to initiation of study treatment, A0) should be provided or preferably a fresh biopsy (S0) can be performed but is not mandatory and collection of an on-treatment biopsy (T1) should be done in at least 10 patients at the recommended dose to assess centrally ER degradation by IHC. Day of collection of biopsy under treatment should be at the end of Cycle 2 (D15 to D28) (➔). Time of sampling in relation to dose administration should be noted.

d Plasma will be collected in all patients to monitor mutational profiling of the tumor in cfDNA by NGS, at baseline (CF00) and at the EOT (CF01).

e Saliva (germline DNA): Saliva will be collected at baseline (SA00) to extract germline DNA which will be used as a reference to determine tumor somatic mutations in CfDNA

f Plasma (ER00) will be collected at baseline and (ER001) at end of Cycle 2 (D15 to D28) to determine the ESR1 mutation status in cfDNA by droplet digital PCR.

g One PK sample will be collected just after tumor assessment (CT/MRI scan) in Cycle 2 (P10), Cycle 4 (P11) and Cycle 6 (P12). No sample will be collected after Part B cut-off date.

Note: For the comfort of patients, some PK samplings may be deleted during the course of the study if they are no longer deemed necessary by the Sanofi PK team

CfDNA = circulating free DNA; DMET = drug metabolizing enzymes and transporters; EOT = end of treatment; ESR1 = estrogen receptor 1; FFPE = formalin-fixed paraffin-embedded; NGS=Next Generation Sequencing; PCR = polymerase chain reaction; PK = pharmacokinetics.

1.4.2 Arm #2

1.4.2.1 Parts C and D

Study treatment in Parts C and D, Cycle 1, Day 1 should not be initiated on a Monday.

The following flow chart in Section 1.4.2.1.1 and Section 1.4.2.1.2 represents the option when amcenestrant is administered concomitantly with food and concomitantly with palbociclib.

In Part D, selected dose(s) will be sampled according to the following full PK/PD flow chart in Section 1.4.2.1.1.

The remaining patients of the cohort will be sampled according to a sparse PK/PD flow chart presented in Section 1.4.2.1.2.

1.4.2.1.1 Part C and D full PK sampling

Cycle	**PARTS C and D Cycle 1**											
Day within cycle	**Day 1/2**										**Day 8**	**Day 15**
Relative Nominal Time	**0 h**	**0.5 h**	**1 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**10 h**	**24 h**	**0 h**	**0 h**
Time window	**[-10 min, 0 h]**	**±5 min**	**±10 min**	**±15 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±1 h**	**±1 h**	**[-10 min, 0 h]**	**[-10 min, 0 h]**
Indicative clock time	08:00	08:30	09:00	10:00	11:00	12:00	14:00	16:00	18:00	08:00	08:00	08:00
Amcenestrant administration[a]												
Once or twice daily	X									X	X	X
Palbociclib administration												
Once daily for 21 days	X									X	X	X
Amcenestrant pharmacokinetics[g]												
Plasma	P00[b]	P01	P02	P04	P05	P06	P07	P08	P09	P10[b]	P11[b]	P12[b]
Palbociclib pharmacokinetics												
Plasma	PP00[b]	PP01	PP02	PP04	PP05	PP06	PP07	PP08	PP09	PP10[b]	PP11[b]	PP12[b]
Pharmacogenetics (DMET genotyping)												
DMET analysis	B00[b]											
Pharmacodynamics												
Plasma (cfDNA-NGS mutational profiling)[c]	CF00											
Saliva (germline DNA)[e]	SA00											
Plasma (cfDNA-ESR1 by dd-PCR)[d]	ER00											
Serum (Estradiol)[h]	ES00											

Cycle	PARTS C and D Cycle 1										Cycle 2		EOT
Day within cycle	**Day 21/22**										**Day 1**	**Day 15 to Day 28**	**Day 30**
Relative Nominal Time	**0 h**	**0.5 h**	**1 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**10 h**	**24 h**	**0 h**		
Time window	**[-10 min, 0 h]**	**±5 min**	**±10 min**	**±15 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±1 h**	**±1 h**	**[-10 min, 0 h]**		
Indicative clock time	08:00	08:30	09:00	10:00	11:00	12:00	14:00	16:00	18:00	08:00	08:00		
Amcenestrant administration[a]													
Once or twice daily	X									X	X		
Palbociclib administration													
Once daily for 21 days	X [f]										X		
Amcenestrant pharmacokinetics[g]													
Plasma	P13[b]	P14	P15	P17	P18	P19	P20	P21	P22	P23[b]	P24[b]		
Palbociclib pharmacokinetics													
Plasma	PP13[b]	PP14	PP15	PP17	PP18	PP19	PP20	PP21	PP22	PP23[b]	PP24[b]		
Pharmacodynamics													
Plasma (cfDNA-ESR1)[d]												ER001	
Plasma (cfDNA – NGS mutational profiling)[c]													CF01
Saliva germline (DNA)[e]													
Serum (Estradiol) [h]												ES01	

a On basis of PK information from the pilot food effect in Part A and safety information, amcenestrant will be taken together with palbociclib, ie, with food, 5 minutes apart, regardless of the order of intake on Day 1 and Day 21/22 (days with full PK sampling) in Cycle 1. Amcenestrant will be taken with food together with palbociclib, 5 minutes apart, regardless of the order of intake.

b Sample collected just before amcenestrant and palbociclib administration.

c Plasma will be collected in all patients to monitor the molecular profile of the tumor in cfDNA at baseline (CF00) and at the EOT (CF01).

d Plasma will be collected at baseline and at end of Cycle 2 (D15 to D28) to determine the ESR1 mutation status in cfDNA by droplet digital PCR (ER00, ER001).

e Saliva germline mutation analysis**:** Saliva will be collected at baseline (SA00) to extract germline DNA which will be used as a reference to determine tumor somatic mutations in CfDNA.

f Last day of palbociclib administration for cycle 1.

g In case of twice daily regimen, Day 1 24 h sample and Day 21/22 24 h sample are not mandatory.

h Estradiol will be assessed in Part D only.

Note: For the comfort of patients, some PK samplings may be deleted during the course of the study if they are no longer deemed necessary by the Sanofi PK team.

CfDNA = circulating free DNA; EOT = end of treatment; ESR1 = estrogen receptor 1; PCR = polymerase chain reaction; PK = pharmacokinetics

1.4.2.1.2 Part D sparse PK sampling

Cycle	PARTS D Cycle 1										Cycle 2		EOT
Day within cycle	**Day 1**				**Day 8**	**Day 15**	**Day 21**				**Day 1**	**Day 28**	**Day 30**
Time window		**[1 h - 2 h]**	**[3 h - 5 h]**	**[7 h - 9 h]**	**[-10 min, 0 h]**	**[-10 min, 0 h]**	**[-10 min, 0 h]**	**[1 h - 2 h]**	**[3 h - 5 h]**	**[7 h - 9 h]**	**[-10 min, 0 h]**		
Indicative clock time	08:00	[09:00 - 10:00]	[11:00 - 13:00]	[15:00 - 17:00]	08:00	08:00	08:00	[09:00 - 10:00]	[11:00 - 13:00]	[15:00 - 17:00]	08:00		
Amcenestrant administration[a]													
Once or twice daily	X				X	X	X				X		
Palbociclib administration[a]													
Once daily for 21 days	X				X	X	X[e]				X		
Amcenestrant pharmacokinetics													
Plasma		P00	P01	P02	P03[b]	P04[b]	P05[b]	P06	P07	P08	P09[b]	P10[f]	
Palbociclib pharmacokinetics													
Plasma		PP00	PP01	PP02	PP03[b]	PP04[b]	PP05[b]	PP06	PP07	PP08	PP09[b]	PP10	
Pharmacogenetics (DMET genotyping)													
DMET analysis	B00[b]												
Pharmacodynamics													
Plasma (cfDNA-NGS mutation profiling)[c]	CF00												CF01
Saliva (germline DNA)[c]	SA00												
Plasma (cfDNA-ESR1 by dd-PCR)[d]	ER00											ER001	
Serum (Estradiol)	ES00											ES01	

a Amcenestrant will be taken with palbociclib in fed condition, 5 minutes apart, regardless of the order of intake.
b Sample collected just before amcenestrant and palbociclib administration.
c Plasma will be collected in all patients to monitor molecular profile of the tumor in cfDNA at baseline (CF00) and at the EOT (CF01). Saliva will be collected at baseline (SA00) to extract germline DNA which will be used as a reference to determine tumor somatic mutations in CfDNA.
d Plasma will be collected at baseline and at end of Cycle 2 (D15 to D28) Cycle 2 to determine the ESR1 mutation status in cfDNA by droplet digital PCR (ER00, ER001).
e Last day of palbociclib administration for Cycle1.
f One PK sample will be collected just after tumor assessment (CT/MRI scan) in Cycle 2 (P10), Cycle 4 (P11) and Cycle 6 (P12). No sample will be collected after Part D cut-off date.
Note: For the comfort of patients, some PK samplings may be deleted during the course of the study if they are no longer deemed necessary by the Sanofi PK team.
CfDNA = circulating free DNA; EOT = end of treatment; ESR1 = estrogen receptor 1; PCR = polymerase chain reaction; PK = pharmacokinetics.

1.4.3 Arm #3

1.4.3.1 Part F and G

Plasma (cfDNA – Next Generation Sequencing (NGS) mutational profiling) will be collected predose at screening, end of Cycle 2 and Cycle 4 (at tumor assessment) and at EOT/progression (whichever comes first). This NGS targeted panel measures genomic aberrations of *PIK3CA*, ESR1 and other tumor driver genes.

ESR1 targeted digital droplet PCR panel from plasma cfDNA will not be collected or analyzed. ESR1 mutations will be analyzed by means of plasma cfDNA broader mutational profiling NGS panel.

Biopsy: When patients consent for paired biopsies, a tumor sample is required in the screening period: either the most recent FFPE tumor specimen should be provided or preferably a fresh biopsy (S0) can be performed but is not mandatory. The day of collection of biopsy under treatment should be at the end of Cycle 2 (D15 to D28, at the tie of tumor assessment). The time of sampling in relation to dose administration should be noted

All patients from the safety run-in will be sampled according to full PK sampling design (Section 1.4.3.1.1) for amcenestrant and alpelisib. At the RD in the expansion phase, additional patients will be sampled according to full PK sampling to reach a total (safety run-in + expansion) of approximately 18 evaluable patients. For the remaining patients of the expansion phase, a sparse sampling approach for PK of amcenestrant will be proposed as presented in Section 1.4.3.1.2.

1.4.3.1.1 Full PK sampling (Parts F and G)

A total of 18 patients (including Part F and G) could undergo a full PK sampling schedule at the recommended dose(s) assessed in Part G. Adjustment of the number of patients needed will be done according to preliminary PK results.

Cycle	**Screening**	**PARTS F and G Cycle 1**										
Day within cycle		**Day 3 (3rd administration of alpelisib's first administration)**									**Day 8**	**Day 15**
Relative Nominal Time		**0 h**	**1 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**10 h**	**24 h**	**0 h**	**0 h**
Time window		**[-10 min, 0 h]**	**±10 min**	**±15 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±1 h**	**±1 h**	**[-10 min, 0 h]**	**[-10 min, 0 h]**
Indicative clock time		08:00	09:00	10:00	11:00	12:00	14:00	16:00	18:00	08:00	08:00	08:00
Amcenestrant administration[a]												
Once daily										X	X	X
Alpelisib administration												
Once daily		X[e]								X	X	X
Amcenestrant pharmacokinetics												
Plasma											P00[b]	P01[b]
Alpelisib pharmacokinetics												
Plasma		P00[b]	P01	P02	P03	P04	P05	P06	P07	P08[b]	P09[b]	P10[b]
Pharmacogenetics (DMET genotyping)												
DMET analysis		B00[b]										
Pharmacodynamics												
Plasma (cfDNA-NGS mutation profiling)[c]	CF00											
Saliva (germline DNA)[d]		SA00										
Tumor biopsy[f]	S0											
Serum (Estradiol)		ES00										

Cycle	PARTS F and G Cycle 1									Cycle 2		Cycle 4	EOT
Day within cycle	Day 22 +/- 2									Day 1	Day 15 to Day 28	Day 28	Day 30
Relative Nominal Time	0 h	1 h	2 h	3 h	4 h	6 h	8 h	10 h	24 h	0 h			
Time window	[-10 min, 0 h]	±10 min	±15 min	±15 min	±30 min	±30 min	±30 min	±1 h	±1 h	[-10 min, 0 h]			
Indicative clock time	08:00	09:00	10:00	11:00	12:00	14:00	16:00	18:00	08:00	08:00			
Amcenestrant administration[a]													
Once daily	X								X	X			
Alpelisib administration													
Once daily	X								X	X			
Amcenestrant pharmacokinetics													
Plasma	P02[b]	P03	P04	P05	P06	P07	P08	P09	P10[b]	P11 [b]			
Alpelisib pharmacokinetics													
Plasma	P11[b]	P12	P13	P14	P15	P16	P17	P18	P19[b]	P20[b]			
Pharmacodynamics													
Plasma (cfDNA -NGS mutational profiling)[c]											CF01	CF02	CF03
Saliva germline (DNA)[d]													
Tumor biopsy[f]											T1		
Serum (Estradiol)											ES01		

a Amcenestrant will be taken with alpelisib in fed condition, QD from C1D4. The days of PK assessment *ie,* C1D1 and C1D22, the drugs will have to be taken with a standard breakfast.

b Sample collected just before amcenestrant and/or alpelisib administration.

c Plasma will be collected in all patients to monitor the molecular profile of the tumor in cfDNA at Screening (CF00), end of Cycle 2 (CF01) and 4 (CF02) (at the time of tumor assessment) and at the EOT/progression (CF03). Analysis of mutational profiling will be done by Next Generation Sequencing (NGS) in reference to the sequence of germline DNA extracted from saliva (S00).

d Saliva germline mutation: Saliva will be collected at baseline (SA00) to extract germline DNA which will be used as a reference to determine tumor somatic mutations in CfDNA.

e Alpelisib will be administrated once daily alone,in fed condition, without amcenestrant for 3 days and then in combination with amcenestrant.

f When patients consent for paired biopsies, a tumor sample is requested at screening: either the most recent FFPE tumor specimen (no time limitation, A0) should be provided or preferably a fresh biopsy (S0) can be performed but is not mandatory and collection of an on-treatment biopsy (T1) will be requested. Day of collection of biopsy under treatment should be at the end of Cycle 2 (between D15 to D28 at tumor assessment). Time of sampling in relation to dose administration should be noted.

Note: For the comfort of patients, some PK samplings may be deleted during the course of the study if they are no longer deemed necessary by the Sanofi PK team.

CfDNA = circulating free DNA; EOT = end of treatment; ESR1 = estrogen receptor 1; PCR = polymerase chain reaction; PK = pharmacokinetics; NGS= Next Generation Sequencing

1.4.3.1.2 Sparse PK sampling (Remaining patients in Part G)

Cycle	Screening	Part G Cycle 1										Cycle 2		Cycle 4	EOT
Day within cycle		Day 1				Day 8	Day 15	Day 22				Day 1	Day 28	28 day	Day 30
Time window			[1 h - 2 h]	[3 h - 5 h]	[7 h - 9 h]	[-10 min, 0 h]	[-10 min, 0 h]	[-10 min, 0 h]	[1 h - 2 h]	[3 h - 5 h]	[7 h - 9 h]	[-10 min, 0 h]			
Indicative clock time		08:00	[09:00 - 10:00]	[11:00 - 13:00]	[15:00 - 17:00]	08:00	08:00	08:00	[09:00 - 10:00]	[11:00 - 13:00]	[15:00 - 17:00]	08:00			
Amcenestrant administration[a]															
Once						X	X	X				X			
Alpelisib administration[a]															
Once		X				X	X	X				X			
Amcenestrant pharmacokinetics															
Plasma[c]						P01[b]	P02[b]	P03[b]	P04	P05	P06	P07[b]	P08[c]	P09[c]	
Pharmacogenetics (DMET genotyping)															
DMET analysis		B00[b]													
Pharmacodynamics															
Plasma (cfDNA-NGS mutational profiling)[d]	CF00												CF01	CF02	CF03
Saliva (germline DNA)[d]		SA00													
Tumor biopsy[e]	S0												T1		
Serum (Estradiol)		ES00											ES01		

a Amcenestrant will be taken with alpelisib in fed condition.
b Sample collected just before amcenestrant and alpelisib administration.
c One PK sample will be collected just after tumor assessment (CT/MRI scan) in Cycle 2 (P08), Cycle 4 (P09) and Cycle 6 (P10). No sample will be collected after Part G cut-off date.
d Plasma will be collected in all patients to monitor molecular profile of the tumor in cfDNA at screening (CF00), end of Cycle 2 (CF01) and Cycle 4 (CF02) (same day as tumor assessment) and at the EOT/progression (CF03). Analysis of mutational profiling will be done by NGS in reference to the sequence of germline DNA extracted from saliva (SA00).
e When patients consent for paired biopsies, a tumor sample is requested at screening: either the most recent FFPE tumor specimen (no time limitation, A0) should be provided or preferably a fresh biopsy (S0) can be performed but is not mandatory and collection of an on-treatment biopsy (T1) will be requested. Day of collection of biopsy under treatment should be at the end of Cycle 2 (between D15 to D28 at tumor assessment). Time of sampling in relation to dose administration should be noted.

Note: For the comfort of patients, some PK samplings may be deleted during the course of the study if they are no longer deemed necessary by the Sanofi PK team.
CfDNA = circulating free DNA; EOT = end of treatment; ESR1 = estrogen receptor 1; PCR = polymerase chain reaction; PK = pharmacokinetics; NGS= Next Generation Sequencing, FFPE = formalin-fixed paraffine-embedded

1.4.4 Arm #4

1.4.4.1 Parts H and I

When the dose escalation study (Part H) completes, based on preliminary safety, PK and tumor response data, the Study Committee will decide or not to expand the combination to Part I with approximately 12 patients.

Cycle	**Screening**	**PARTS H and I, Cycle 1**								
Day within cycle		**Day 1**								
Relative Nominal Time		**0 h**	**1 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**10 h**	**24 h**
Time window		**[-10 min, 0 h]**	**±10 min**	**±15 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±1 h**	**±1 h**
Indicative clock time		8:00	9:00	10:00	11:00	12:00	14:00	16:00	18:00	8:00
IMP administration [a]										
Amcenestrant, QD		X								X
Everolimus, QD		X								X
Pharmacokinetics samples										
Amcenestrant, Plasma		P00[b]	P01	P02	P03	P04	P05	P06	P07	P08[b]
Everolimus, Blood		BE00[b]	BE01	BE02	BE03	BE04	BE05	BE06	BE07	BE08[b]
Pharmacogenetics (DMET genotyping)										
DMET analysis		B00[b]								
Pharmacodynamics										
Plasma (cfDNA -NGS mutational profiling)[c]	CF00									
Saliva germline (DNA)[d]		SA00								
Tumor biopsy[e]	S0									
Serum (Estradiol)[f]		ES00								

Cycle	PARTS H and I, Cycle 1									Cycle 2		Cycle 4	EOT
Day within cycle	Day 22 ± 2									Day 1	Day 28	Day 28	Day
Relative Nominal Time	0 h	1 h	2 h	3 h	4 h	6 h	8 h	10 h	24 h	0 h			
Time window	[-10 min, 0 h]	±10 min	±15 min	±15 min	±30 min	±30 min	±30 min	±1 h	±1 h	[-10 min, 0 h]			
Indicative clock time	8:00	9:00	10:00	11:00	12:00	14:00	16:00	18:00	8:00	8:00			
IMP administration [a]													
Amcenestrant, QD	X								X	X			
Everolimus, QD	X								X	X			
Pharmacokinetics samples													
Amcenestrant, Plasma	P09[b]	P10	P11	P12	P13	P14	P15	P16	P17[b]	P18[b]			
Everolimus, Blood	BE09[b]	BE10	BE11	BE12	BE13	BE14	BE15	BE16	BE17[b]	BE18[b]			
Pharmacodynamics													
Plasma (cfDNA -NGS mutational profiling)[c]											CF01	CF02	CF03
Saliva germline (DNA)[d]													
Tumor biopsy[e]											T1		
Serum (Estradiol)[f]											ES01		

a Amcenestrant and everolimus will be taken with food, once daily (QD), together, 5 minutes apart. The days of PK assessment *ie,* C1D1 and C1D22, the drugs will have to be taken with a standard breakfast.

b Sample collected just before amcenestrant and everolimus administration

c Plasma will be collected in all patients to monitor the molecular profile of the tumor in cfDNA at Screening (CF00), end of Cycle 2 (CF01) and 4 (CF02) (at the time of tumor assessment) and at the EOT/progression (CF03). Analysis of mutational profiling will be done by Next Generation Sequencing (NGS) in reference to the sequence of germline DNA extracted from saliva (S00).

d Saliva germline mutation: Saliva will be collected at baseline (SA00).

e When patients consent for paired biopsies, a tumor sample is requested at screening: either the most recent FFPE tumor specimen (no time limitation, A0) should be provided or preferably a fresh biopsy (S0) can be performed but is not mandatory and collection of an on-treatment biopsy (T1) will be requested. Day of collection of biopsy under treatment should be at the end of Cycle 2 (between D15 to D28 at tumor assessment). Time of sampling in relation to dose administration should be noted.

f Estradiol will be assessed in Part I only

Note: For the comfort of patients, some PK samplings may be deleted during the course of the study if they are no longer deemed necessary by the Sanofi PK team.

CfDNA = circulating free DNA; EOT = end of treatment; ESR1 = estrogen receptor 1; PCR = polymerase chain reaction; PK = pharmacokinetics; NGS= Next Generation Sequencing

1.4.5 Arm #5

1.4.5.1 Parts J and K

When the dose escalation study (Part J) completes, based on preliminary safety, PK and efficacy data, the Study Committee will decide or not to expand the combination to Part K with approximately 20 patients. In Part K, up to 12 patients could undergo a full PK sampling (Section 1) to allow a total of 15 evaluable patients under a full PK sampling, overall Part J and Part K. The remaining patients of Part K, will undergo a sparse PK sampling approach (Section 1.4.5.1.2).

1.4.5.1.1 Parts J and K, full PK sampling

Cycle	**Screening**	**PARTS J and K, Cycle 1**								
Day within cycle		**Day 1**								
Relative Nominal Time		**0 h**	**1 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**10 h**	**24 h**
Time window		**[-10 min, 0 h]**	**±10 min**	**±15 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±1 h**	**±1 h**
Indicative clock time		8:00	9:00	10:00	11:00	12:00	14:00	16:00	18:00	8:00
IMP administration[a]										
Amcenestrant, QD		X								X
Abemaciclib, BID		X								X
Pharmacokinetics samples										
Amcenestrant, Plasma		P00[b]	P01	P02	P03	P04	P05	P06	P07	P08[b]
Abemaciclib and metabolites, Plasma		P00[b]	P01	P02	P03	P04	P05	P06	P07	P08[b]
4β-hydroxycholesterol /total cholesterol		P00[b]								
Pharmacogenetics (DMETgenotyping)										
DMET analysis		B00[b]								
Pharmacodynamics										
Plasma (cfDNA -NGS mutational profiling)[c]	CF00									
Saliva germline (DNA)[d]		SA00								
Tumor biopsy[e]	S0									
Serum (Estradiol)[f]		ES00								

Cycle	PARTS J and K, Cycle 1									Cycle 2			Cycle 3	Cycle 4	EOT
Day within cycle	Day 22 ± 2									Day 1		Day 28	Day 1	Day 28	Day
Relative Nominal Time	0 h	1 h	2 h	3 h	4 h	6 h	8 h	10 h	24 h	0 h	4 h		0 h		
Time window	[-10 min, 0 h]	±10 min	±15 min	±15 min	±30 min	±30 min	±30 min	±1 h	±1 h	[-10 min, 0 h]	±30 min		[-10 min, 0 h]		
Indicative clock time	8:00	9:00	10:00	11:00	12:00	14:00	16:00	18:00	8:00	8:00	12:00		8:00		
IMP administration[a]															
Amcenestrant, QD	X								X	X			X		
Abemaciclib, BID	X								X	X			X		
Pharmacokinetics samples															
Amcenestrant, Plasma	P09[b]	P10	P11	P12	P13	P14	P15	P16	P17*b*	P18[b]	P19				
Abemaciclib and metabolites, Plasma	P09[b]	P10	P11	P12	P13	P14	P15	P16	P17*b*	P18[b]	P19				
4β-hydroxycholesterol /total cholesterol										P01[b]		P02[b]			
Pharmacodynamics															
Plasma (cfDNA -NGS mutational profiling)[c]												CF01		CF02	CF03
Saliva germline (DNA)[d]															
Tumor biopsy[e]												T1			
Serum (Estradiol)[f]												ES01			

a Amcenestrant will be taken once daily, and abemaciclib twice daily (BID), both taken with food during the study. The days of PK assessment (ie, C1D1 and C1D22) the drugs will have to be taken after a standard breakfast

b Sample collected just before amcenestrant and abemaciclib administration

c Plasma will be collected in all patients to monitor the molecular profile of the tumor in cfDNA at Screening (CF00), end of Cycle 2 (CF01) and 4 (CF02) (at the time of tumor assessment) and at the EOT/progression (CF03). Analysis of mutational profiling will be done by Next Generation Sequencing (NGS) in reference to the sequence of germline DNA extracted from saliva (SA00).

d Saliva germline mutation: Saliva will be collected at screening (SA00) to extract germline DNA which will be used as a reference to determine tumor somatic mutations in CfDNA.

e When patients consent for paired biopsies, a tumor sample is requested at screening: either the most recent FFPE tumor specimen (no time limitation, A0) should be provided or preferably a fresh biopsy (S0) can be performed but is not mandatory and collection of an on-treatment biopsy (T1) will be requested. Day of collection of biopsy under treatment should be at the end of Cycle 2 (between D15 to D28 at tumor assessment). Time of sampling in relation to dose administration should be noted.

f Estradiol will be assayed in Part K only

Note: For the comfort of patients, some PK samplings may be deleted during the course of the study if they are no longer deemed necessary by the Sanofi PK team.

CfDNA = circulating free DNA; EOT = end of treatment; ESR1 = estrogen receptor 1; PCR = polymerase chain reaction; PK = pharmacokinetics; NGS= Next Generation Sequence

1.4.5.1.2 Part K, sparse PK sampling

Cycle	Screening	Part K Cycle 1								Cycle 2			Cycle 4	EOT
Day within cycle		Day 1			Day 8	Day 15	Day 22			Day 1		Day 28		Day 30
Time window			[1 h - 2 h]	[3 h - 5 h]	[-10 min, 0 h]	[-10 min, 0 h]	[-10 min, 0 h]	[1 h - 2 h]	[3 h - 5 h]	[-10 min, 0 h]	[7 h - 9 h]			
Indicative clock time		08:00	[09:00 - 10:00]	[11:00 - 13:00]	08:00	08:00	08:00	[09:00 - 10:00]	[11:00 - 13:00]	08:00	[15:00 - 17:00]			
IMP administration[a]														
Amcenestrant, QD		X			X	X	X			X				
Abemaciclib, BID		X			X	X	X			X				
Pharmacokinetics samples														
Amcenestrant, Plasma			P00	P01	P02[b]	P03[b]	P04[b]	P05	P06	P07[b]	P08	P09[c]		
Abemaciclib, Plasma			P00	P01	P02[b]	P03[b]	P04[b]	P05	P06	P07[b]	P08	P09[c]		
Pharmacogenetics														
DMET analysis		B00[b]												
Pharmacodynamics														
Plasma (cfDNA-NGS mutational profiling)[d]	CF00											CF01	CF02	CF03
Saliva (germline DNA)[d]		SA00												
Tumor biopsy[e]	S0											T1		
Serum (Estradiol)		ES00										ES01		

a Amcenestrant will be taken once daily (QD), and abemaciclib twice daily (BID), both taken with food The days of PK assessment (ie, C1D1 and C1D22) the drugs will have to be taken after a standard breakfast.
b Sample collected just before amcenestrant and abemaciclib administration.
c One PK sample will be collected just after tumor assessment (CT/MRI scan) in Cycle 2, Cycle 4 and Cycle 6. No sample will be collected after Part K cut-off date.
d Plasma will be collected in all patients to monitor molecular profile of the tumor in cfDNA at screening (CF00), end of Cycle 2 (CF01) and Cycle 4 (CF02) (same day as tumor assessment) and at the EOT/progression (CF03). Analysis of mutational profiling will be done by NGS in reference to the sequence of germline DNA extracted from saliva (SA00).
e When patients consent for paired biopsies, a tumor sample is requested at screening: either the most recent FFPE tumor specimen (no time limitation, A0) should be provided or preferably a fresh biopsy (S0) can be performed but is not mandatory and collection of an on-treatment biopsy (T1) will be requested. Day of collection of biopsy under treatment should be at the end of Cycle 2 (between D15 to D28 at tumor assessment). Time of sampling in relation to dose administration should be noted.

Note: For the comfort of patients, some PK samplings may be deleted during the course of the study if they are no longer deemed necessary by the Sanofi PK team.
CfDNA = circulating free DNA; EOT = end of treatment; ESR1 = estrogen receptor 1; PCR = polymerase chain reaction; PK = pharmacokinetics; NGS= Next Generation Sequencing, FFPE = formalin-fixed paraffine-embedded

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2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

18FDG:	18fluorodesoxyglucose (18F)
18F-FES:	18F-fluorestradiol
ADME:	absorption, distribution, metabolism, excretion
AE:	adverse events
AIs:	aromatase inhibitors
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANC:	absolute neutraphil count, absolute neutraphil count
aPTT:	activated partial thromboplatin time
AST:	aspartate aminotransferase
ATC:	anatomical, therapeutic, and chemical
AUC_{0-24}:	area under the plasma concentration versus time curve from time zero to 24 hours
BID:	twice daily
BUN:	blood urea nitrogen
CDK:	cyclin dependent kinase
cfDNA:	circulating free DNA
COD:	cut-off date
CR:	complete response
CSR:	clinical study report
CT:	computerized tomography
C_{trough}:	plasma concentration observed before treatment administration
CYP:	cytochrome P450
ddPCR:	droplet digital polymerase chain reaction
DLT:	dose-limiting toxicity
DMET:	drug metabolizing enzyme and transporters
DRESS:	drug reaction with eosinophilia and systemic symptoms
DRF:	discrepancy resolution form
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
EM:	erythema multiforme
EOT:	end of treatment
ER:	estrogen receptor
ERα:	estrogen receptor alpha
ESR1:	estrogen receptor 1
F%:	oral bioavailability
FFPE:	formalin-fixed paraffine-embedded
FSH:	follicle stimulating hormone
GCP:	Good Clinical Practice
GGT:	gamma glutamyl transferase
GLP:	Good Laboratory Practice
GnRH:	gonadotrophin-releasing hormone

HER2:	human epidermal growth factor receptor 2
HIV:	human immunodeficiency virus
HNSTD:	higher non-severely toxic dose
HR:	hazard ratio
ICF:	informed consent form
ICR:	independent central review
IEC:	Institutional Ethics Committee
IHC:	immunohistochemistry
ILD:	interstitial lung disease
INR:	international normalized ratio
IRB:	Institutional Review Board
LLN:	lower limit of normal, lower limit of normal
MAD:	maximum administered dose
MedDRA:	Medical Dictionary for Regulatory Activities
MRI:	magnetic resonance imaging
MTD:	maximum tolerated dose
NCI-CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS:	next generation sequencing
NOAEL:	no observed adverse effect limit
ORR:	objective response rate
PCR:	polymerase chain reaction
PD:	pharmacodynamics
PET:	positron emission tomography
PFS:	progression-free survival
PI3K:	phosphoinositide 3-kinase
PK:	pharmacokinetic
PR:	partial response
QD:	once daily
RD:	recommended dose
RECIST:	response evaluation criteria in solid tumors
SD:	stable disease
SERD:	selective estrogen receptor down-regulator
SERM:	selective estrogen receptor modulator
SJS:	Stevens-Johnson syndrome
STD10:	severely toxic dose in 10% of the animals
SUV:	standardized uptake value
TEAE:	treatment-emergent adverse event
TEN:	toxic epidermal necrolysis
t_{max}:	time to maximum plasma concentration
UGT:	UDP-glucuronosyltransferase
ULN:	upper limit of normal
US:	United States

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Breast cancer is the most commonly diagnosed cancer and the second leading cause of death in women (1). In the United States (US) in 2015 it was estimated 231 840 new cases of invasive breast cancer as well as 60 290 additional cases of in situ breast cancer would be reported. Approximately 40 290 women were expected to die (2015) from breast cancer (2).

Both endogenous and exogenous steroid hormones such as estrogen and progesterone have been implicated in the pathogenesis of breast cancer. Clinical treatment decisions are driven by the expression of estrogen receptors (ERs), progesterone receptors and human epidermal growth factor receptor 2 (HER2) receptor status into HER2+, ER+/HER2- and triple negative clinical subtypes. About 75% of breast cancers express estrogen receptor alpha (ERα) which is a hormone regulator transcription factor (3). ER-positive breast cancers respond well to therapy targeting ER signaling either through competitive binding of ER antagonists such as tamoxifen or by blocking the production of estrogen by aromatase inhibitors (AIs) (4).

According to guidelines, sequential hormonal therapy (alone or in combination) is the standard of care in the metastatic breast cancer setting for ER-positive, HER2-negative patients without rapidly progressing visceral or symptomatic metastases. Common classes of drugs used for this purpose include selective estrogen receptor modulator (SERM) such as tamoxifen, AIs like letrozole, anastrozole or exemestane, selective estrogen receptor down-regulators (SERD) represented by fulvestrant and luteinizing hormone releasing hormone agonists like buserelin and goserelin.

Unfortunately, not all patients respond to first-line hormonal therapy as they present with primary or de novo resistance, and some patients who initially respond subsequently have breast cancer progression (acquired resistance). Resistance to endocrine therapies is frequent but relapsed tumors remain dependent on ER, which is highlighted by patient responses to second and third line endocrine therapies after failure of an earlier line of hormonal therapy. Estrogen receptor alpha signaling reactivation can occur due to change in ligand sensitivity and specificity or by new mutations of the estrogen receptor 1 (ESR1) (5). Estrogen receptor 1 gene mutation was recently evaluated in clinical studies with a high prevalence (25% to 40%) in relapse patients after AI therapy (6); with a limited benefit with current monotherapy. The continued dependence of breast cancer tumors on ER provides a strong rationale to continue to target ER in both first line and relapsed/advanced settings.

Selective ER down-regulators are competitive ER antagonists that also induce conformational changes that lead to the degradation of ER via an ubiquitin-proteasome system (7). The unique dual function of SERDs (ER antagonism and depletion) may enable them to block ER signaling in cellular settings where other endocrine agents, such as tamoxifen or AIs have failed. The clinical effect of fulvestrant as a treatment for recurrent endocrine-resistant disease supports this matter. Although fulvestrant has served as an important proof of concept for the SERD approach, this therapy is limited by its poor pharmaceutical properties which necessitate intramuscular administration and limits the applied dose, exposure and receptor engagement (8, 9).

The fulvestrant 500 mg regimen (500 mg on Days 1, 14, 28; monthly thereafter) exhibited improvement in progression free survival and overall survival over the initially marketed 250 mg dose (10). However the 500 mg dose of fulvestrant does not fully saturate ER binding in patients as inhibition of 18F-fluorestradiol (18F-FES) positron emission tomography (PET) scan uptake was incomplete in 38% (6/16) of patients. This lack of receptor occupancy was associated with lack of clinical benefit (9, 11).

These data demonstrate that SERDs have the potential to provide effective and well-tolerated therapy for postmenopausal women with advanced breast cancer and highlight the need for the development of new SERDs with optimized characteristics: improved route of administration (oral versus intramuscular route), bioavailability and maintenance of ER receptor blockade combined with a strong antitumor activity.

There is strong efficacy data to support the addition of targeted therapy, including the cyclin dependent kinase (CDK) 4/6 inhibitor or phosphoinositide 3-kinase (PI3K) inhibitor to endocrine therapy for the treatment of ER+/HER2- advanced/metastatic breast cancer. A recent series of studies have evaluated combinations of CDK4/6 inhibitor (palbociclib, abemaciclib, ribociclib), with endocrine therapy and demonstrated significant improvement in both progression-free survival (PFS) and overall survival (OS) compared to endocrine monotherapy in the first and second line settings (12, 13, 14). Abemaciclib was approved in combination with an aromatase inhibitor as initial endocrine based therapy for advanced or metastatic breast cancer and in combination with fulvestrant for advanced or metastatic breast cancer with disease progression following endocrine therapy (15). It was also approved as monotherapy for advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

Advances in treating metastatic BC have focused on improving the efficacy of endocrine therapy by adding agents that target specific molecular pathways of breast cancer cell growth and survival. The combination of the aromatase inhibitor exemestane and the mammalian target of rapamycin inhibitor(mTOR) everolimus, more than doubled PFS compared with exemestane alone. Results according to investigator review: showed median PFS of 7.8 vs 3.2 months, respectively; hazard ratio 0.45 [95% CI: 0.38–0.54]; log rank P <0.0001) in the BOLERO-2 study (14) in 724 postmenopausal women with HR+, HER2- locally advanced or metastatic breast cancer that had recurred or progressed on prior nonsteroidal aromatase inhibitor therapy. According to central review the median PFS was 11.0 versus 4.1 months, respectively; hazard ratio = 0.38 (95% CI: 0.31–0.48); log-rank P<0.0001] in the overall population and in all prospectively defined subgroups, including patients with visceral metastases, patients with recurrence during or within 12 months of completion of adjuvant therapy, and irrespective of age. In addition, everolimus plus exemestane was associated with a manageable safety profile. The results of BOLERO-2 led to regulatory approval of everolimus plus exemestane. Everolimus was approved in treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.

More recently, alpelisib was approved by the FDA based on results from the SOLAR-1 study (16). In this Phase 3 randomized and placebo-controlled study, patients with HR-positive, HER2-negative advanced or metastatic breast cancer who had experienced disease recurrence or progression following the use of an aromatase inhibitor were stratified by the presence or absence of a *PIK3CA* mutation and randomized to receive alpelisib with fulvestrant or placebo with

fulvestrant. The prespecified primary endpoint of SOLAR-1 was locally assessed progression-free survival in the cohort with *PIK3CA*-mutated breast cancer. To note, only 20 of the 341 mutated patients had prior exposure to CDK4/6 inhibitors. In the cohort with *PIK3CA*-mutated breast cancer patients the PFS was 11.0 months in the alpelisib with fulvestrant group compared to 5.7 months in the placebo with fulvestrant group and this difference was statistically significant (hazard ratio for progression or death, 0.65; 95% CI, 0.50 to 0.85; P<0.001). In regards to disease response rate, among patients with measurable disease in the cohort with *PIK3CA*-mutated cancer the overall response rate was 35.7% in the alpelisib with fulvestrant group compared to 16.2% in the placebo with fulvestrant group. In addition to SOLAR-1, preliminary data from the Phase 2 BYLieve study (17), conducted in patients who had experienced disease progression with the use of CDK4/6 inhibitors, indicated a lower ORR (15%) compared to the ORR observed in SOLAR-1 (26.6%).

The ability to measure pharmacodynamics (PD) of endocrine therapy in breast cancer patients has been limited, and mechanisms of resistance are incompletely understood. One tool that holds promise for measuring drug effects in cancer patients is molecular imaging. ^{18}F-FES-PET/CT has been validated as an accurate method for localizing ER-expressing tumors (18, 19) and as a predictive assay for breast cancer endocrine therapy (18, 20, 21). In breast cancer, the uptake of ^{18}F-FES, as measured by standardized uptake value (SUV) on PET, has been shown to correlate with ER expression in biopsy material assayed by in vitro radioligand binding and by immunohistochemistry (IHC) (22), providing evidence of the value of ^{18}F-FES SUV to measure specific binding to ER. ^{18}F-FES uptake in breast cancer metastases declines after therapy with ER blocking agents such as tamoxifen and fulvestrant as well as estrogen-depleting agents such as AIs (23, 24). These studies suggest a role for ^{18}F-FES-PET as a key PD biomarker for breast cancer which can help determine the dosage of ER targeted therapies needed for maximal ER occupancy and/or downregulation (25).

4.1.1 BENEFIT/RISK ASSESSMENT

Detailed information about the known and expected benefits and risks and reasonably expected AEs of amcenestrant may be found in the Investigator's Brochure (IB).

Refer to Summary of Product Characteristics or approved label of IBRANCE® (palbociclib), PIQRAY® (alpelisib), AFINITOR® (everolimus) and VERZENIO® (abemaciclib) for more information on additional benefit /risk when the above drugs are being used in combination within the protocol.

4.1.1.1 Benefit Assessment

Amcenestrant, as a new generation SERD with an expected and almost full inhibition of the ER target, may represent a new therapeutic option with a better benefit/risk ratio than approved endocrine-based treatments. Moreover, preclinical findings and clinical pharmacodynamics show a very high saturation of the ER at the tumor level.

Amcenestrant could provide meaningful benefit to participants with advanced breast cancer who progressed on previous advanced therapeutic options or expressed secondary resistance to the adjuvant endocrine treatment.

4.1.1.2 Risk Assessment

To date, the efficacy and safety data from ongoing studies of amcenestrant support continued clinical development of amcenestrant. Based on non-clinical toxicity study results, completed or ongoing clinical studies in patients and in healthy post-menopausal participants, there have been no important identified risks confirmed so far. The important potential risks as per non-clinical toxicity and in vitro assessments include the following: gastrointestinal (GI) toxicity and complications; hepatotoxicity; photosensitivity; drug-drug Interaction; rash; osteoporosis and fertility impairment. Routine Pharmacovigilance (PV) activities are being conducted to monitor these potential risks associated with amcenestrant. Potential risks are summarized in Table 1.

Table 1 - Amcenestrant Risks

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention: Amcenestrant (SAR439859)		
Gastrointestinal toxicity	AMEERA-1 Arm#1 (Parts A and B): A total of 22 out of 62 patients who received amcenestrant monotherapy (>20 mg QD) developed various GI toxicities considered to be related to amcenestrant, none of them were of Grade ≥3. AMEERA-1 Arm#2 (Parts C and D): A total of 19 out of 39 patients who received 200 mg amcenestrant and palbociclib developed GI toxicities considered to be associated to amcenestrant, none of them were of Grade ≥3. In studies conducted in healthy subjects, there were few single occurrences of GI events considered related to amcenestrant. None of them were of Grade ≥3	Events ≥ Grade 3 are to be closely monitored. Preventive or corrective treatment(s): antiemetics, antidiarrheal.
Hepatotoxicity	Preclinical safety data have shown evidence of hepatotoxicity in repeat dose toxicity study at 100 mg/kg/day in dogs. AMEERA-1 Arm#1 (Parts A and B) / Arm#2 (Parts C and D): No event of hepatotoxicity considered to be related to amcenestrant has been reported. Studies in healthy subjects: In completed or ongoing studies in healthy subjects, 3 subjects developed asymptomatic transient ALT increase ≥ 2 × ULN with amcenestrant 300 mg SD alone or in combination with rifampicin. All occurrences were Grade 1. All events of ALT increase were non serious and spontaneously resolutive.	Monitor LFT in cases of increase of Grade≥3 ALT, listed as AESI in the study. Monitor patients with symptoms/signs suggestive of hepatotoxicity: jaundice, increase of liver function tests (LFT) (ALT, AST, GGT, ALP and bilirubin). Patients with impaired liver function should not be included in the study (Exclusion criteria # 17).
Phototoxicity	A phototoxicity risk for amcenestrant was identified based on the absorption spectrum of the compound and in an in vitro phototoxicity study in 3T3 cells which was confirmed in a repeat dose in vivo mouse phototoxicity study. Within the amcenestrant development program which includes the sun protection measures, cumulatively Grade 1 sunburns were observed only in 2 patients out of an estimated 700 participants exposed so far to amcenestrant doses (from 20 to 1200 mg). The first patient received amcenestrant 150 mg QD and experienced G1 sunburn while being exposed to sun without sun protection and the second patient developed G1 sunburn after amcenestrant 400 mg QD.	Limitation of exposure to sunlight or artificial sunlight is recommended along with the requirement for sun protection measures (wear protective clothing, use a broad-spectrum sunscreen to cover ultra-violet A (UVA) and ultra-violet B (UVB) light exposure when outdoors with frequent re-application as necessary, along with lip balm (sun protection factor [SPF] ≥30).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Rash	In Ameera 2, 1 Grade 2 rash and 1 serious Grade 3 rash maculo-papular were reported in Japanese patients (respectively at 400 mg QD and 300 mg BID). The last event was declared as a DLT. Grade 1 rashes have been reported in global population.	Closely monitor if further risk mitigation/management is required
Osteoporosis	Due to mechanism of action of amcenestrant, there is a theoretical risk of osteoporosis when patients are exposed long-term to amcenestrant. No case of osteoporosis has been reported in amcenestrant program. No long-term observation has been performed.	Monitor DEXA at baseline and follow up every 2 years. Monitor bone markers CTX and P1NP at baseline and every 2 years.
DDI	Amcenestrant effect on other drugs: Amcenestrant is • A moderate inducer of CYP3A based on a midazolam clinical study. • A potential CYP2B6, CYP2Cs and UGTs inducer • A potential inhibitor of OATP1B1/1B3 transporters Effect of other drugs on amcenestrant: • In vitro amcenestrant biotransformation occurs mainly through non-CYP enzymes (around 80% of hepatic clearance) involving UGT1A1 and 1A4. CYP2C8 and CYP3A are involved to less than 20%. • CYP3A clearance was confirmed to be minimal based on an itraconazole interaction clinical study. Atazanavir, a UGT1A1 inhibitor increases amcenestrant exposure by 59 to 74%. • Strong metabolism enzyme inducers (Rifampicin) decrease amcenestrant exposure by 30% No adverse event related to DDI has been reported in clinical studies as of 29 May 2021.	Drugs which are sensitive substrates of CYP3A, CYP2B6, CYP2Cs, and/or UGT should be closely monitored for efficacy. Treatment with drugs that are sensitive substrates of OATP1B1/1B3 (asunaprevir, batorvastatin, bosentan, danoprevir, fexofenadine, glyburide, nateglinide, pitavastatin, pravastatin, repaglinide, rosuvastatin and simvastatin acid) should not be administered with amcenestrant. Drugs that are UGT inhibitors (ie, probenecid, atazanavir) should be used with caution with amcenestrant highest dose (400mg QD). Drugs that are strong inducers of CYP3A should not be administered with amcenestrant. Patients with concomitant medications that are considered to interact with amcenestrant should be excluded (Exclusion criteria # 21)
Study procedures		
Biopsies	It is normal practice to biopsy possible recurrence of breast cancer to (a) confirm diagnosis and (b) check for change of subtype.	When required, biopsies should be done only when tumor is accessible, limiting the risk of Infection or bleeding at the biopsy site. Special caution is needed for patients on anticoagulants, with INR increased, or with thrombocytopenia.

4.1.1.3 Risks in the Context of COVID-19

Cancer patients are at increased risk of contracting SARS-CoV-2 infection and running more severe disease course (26). Cancer encompasses a heterogeneous group of subtypes and stages and the patient's risk profile should therefore be individualized taking into consideration primary tumor type and stage as well as age and sex. The benefit and risk balance of anti-tumor treatments should be also tailored considering the overall treatment goal. For cancer in the curative setting, this risk/benefit balance favors maintaining systemic treatments.

The investigators should always exercise their medical judgement to individualize clinical decisions and adhere to local and institutional guidelines for SARS-CoV-2 infection prevention and vaccine administration.

Testing for SARS-CoV-2 infection during the screening phase should be based on investigator discretion and should also follow local/international guidelines (eg, asymptomatic but high risk of infection patients, patients with symptoms that could be associated with SARS-CoV-2 infection). Patients known to have had SARS-CoV-2 infection prior to study entry must be fully clinically recovered in order to be eligible for participation in the study.

During the study, if a study participant is diagnosed with SARS-CoV-2, dose modification of study intervention should be based on the recommendations provided in Section 6.5. In addition, all investigators are instructed to consult official COVID-19 clinical research guidance from their local hospital/institution along with other relevant resources, such as:

- American society of Clinical Oncology (ASCO) (27)
- European Society for Medical Oncology (ESMO) (28)

Refer to the contingency measures for a regional or national emergency that is declared by a governmental agency detailed in Section 19 (Appendix J)

- It is important to minimize the risk of exposure of patients to COVID-19. In addition to the contingency measures described in Section 19 following prevention and mitigation plans could be implemented at clinical sites. Such plans may include: All participating sites should have implemented measures according to regional/local Health Authorities, European medicines agency (EMA), ESMO, ASCO guidelines including but not limited to restrictions of access to the hospitals for visitors, physical distancing and personal protective equipment (PPE).
- Study participants should be treated in a dedicated area that is separated from patients with COVID-19 infection.

4.1.1.4 Overall Benefit/Risk Conclusion

The benefit-to-risk assessment in patients with advanced breast cancer is still deemed to be acceptable within the context of the AMEERA-1 study, including during the COVID-19 pandemic. This is based on the amcenestrant experience and the observed safety profile in this and other ongoing AMEERA studies, as well as the safety precautions that have been established to safeguard the wellbeing of the participants. Sponsor will continue to evaluate benefit-risk during the study period.

Refer to Summary of Product Characteristics or approved label of IBRANCE® (palbociclib), PIQRAY® (alpelisib), AFINITOR® (everolimus) and VERZENIO® (abemaciclib) for more information on additional benefit /risk information.

4.2 DESCRIPTION OF AMCENESTRANT

Amcenestrant is an optimized oral selective estrogen receptor degrader (SERD) with dual activity which antagonizes and degrades the ER, resulting in inhibition of the ER signaling pathway. These dual properties translate into a deeper inhibition of ER pathways and more effective antiproliferative activity in ER‒dependent breast cancer cell lines driven by mutant or wild type ER compared to fulvestrant.

4.3 BACKGROUND INFORMATION OF AMCENESTRANT

Please refer to the Investigator Brochure for more detailed information.

4.3.1 Preclinical data

In vitro pharmacology

Amcenestrant inhibits the activity of both ER wild type and ER mutants (Y537S, D538G). Amcenestrant demonstrates potent antiproliferative activity in ER-positive dependent breast cancer cell lines with IC_{50} of 0.4 nM in MCF7 cells and in mutated MCF7 cells (Y537S=10 nM, D538G=1 nM). Amcenestrant antagonizes the binding of estradiol to ER but also induces receptor degradation (98%) in MCF7 cells (IC_{50}=0.2 nM).

The ER degrading activity of amcenestrant was compared to its direct competitors and reference compounds such as fulvestrant in a panel of 13 breast cancer cell lines. Amcenestrant shows strong ER degradation activity that is comparable to fulvestrant but superior to the SERD competitors, ARN810, AZD9496, and RAD1901.

In vivo pharmacology

At a large range of tolerated doses, amcenestrant demonstrated in vivo tumor regression of ER-positive breast cancer xenograft models including: hormone sensitive (MCF7), ER mutant driven (MCF7- ERY537S) and ET resistant PDX models (HCI 013).

Initial preclinical experiments on ER-positive breast cancer tumor model MCF7 expressing the mutant ER Y537S have demonstrated that ^{18}F-FES-PET imaging is a quantitative assay. Extinction of standard uptake values signal in ^{18}F-FES-PET was shown to match ER degradation as detected with classical ER IHC.

Amcenestrant was evaluated in combination efficacy with CDK4/6 inhibitor palbociclib in MCF7-Y537S xenograft tumor model in nude mice. Either amcenestrant at 5 mg/kg twice a day or palbociclib 100 mg/kg once a day orally as a monotherapy treatment achieved minimal or moderate effect on the tumor growth (%ΔT/ΔC: 59 and 27 respectively), but when combined both together the combination effect demonstrated strong antitumor efficacy and induced tumor regression (%ΔT/ΔC: -32).

Toxicology

Amcenestrant was tested in a variety of in vitro and in vivo studies to identify potential safety issues, determine the safe threshold of exposure in rat and dog as well as target organs of toxicity. Genotoxicity and safety pharmacology liabilities were not identified for amcenestrant.
A phototoxicity liability has been determined for amcenestrant. The no observed adverse effect limit (NOAEL) for phototoxicity was 10 mg/kg/day in a repeat dose study in mice.

Amcenestrant has been tested in repeat dose toxicity studies in rat and dog. A NOAEL could not be established in the 4-week toxicity studies in rat and dog with 4-week recovery. Findings <30 mg/kg/day in both species can be attributed to the antiestrogenic mechanism of action of amcenestrant. The severely toxic dose in 10% of the animals (STD10) in the rat 4-week repeat dose toxicity study with 4-week recovery was >100 mg/kg/day. Target organs of toxicity were ovary, pituitary gland, adrenal gland, and bone.

The higher non-severely toxic dose (HNSTD) in the 4 week repeat dose toxicity study in dogs with 4-week recovery was 30 mg/kg/day in the female. The HNSTD could not be determined in male dogs due to the incomplete recovery of the findings in the testis and epididymis. Target organs of toxicity in the dog were liver, kidney, stomach, ovary and testis/epididymis.

Metabolism and preclinical pharmacokinetics

In animals, amcenestrant generally showed a rapid oral absorption (time to maximum plasma concentration [t_{max}] ~2 to 4 hours) which was longer (up to 24 hours) at higher doses (>100 mg/kg). The oral bioavailability (F%) in mice, rats and dogs was high to moderate with 62%, 76% and 44%, respectively. Following single administration from 3 to 100 mg/kg/day in rats and dogs, area under the plasma concentration versus time curve from time zero to 24 hours (AUC_{0-24}) increased about 2-times more than expected by dose proportionality. After 14-day or 1-month repeated daily administrations in the 3 to 300 mg/kg dose range, no accumulation, nor sex effect were observed.

Amcenestrant was highly bound to plasma proteins and no significant inter-species differences in plasma free fraction were evidenced, including human. The blood over plasma ratio showed no specific affinity to blood in animals or human. The compound showed a moderate volume of distribution in rats (0.8 L/kg) and dogs (0.5 L/kg) but a large volume of distribution in mice (6.1 L/kg).

Amcenestrant inter-species in vitro metabolic profiling in mouse, rat, dog and human hepatocytes revealed a high biotransformation rate of amcenestrant in human, moderate in rat and low in mouse and dog. Phase II glucuronide metabolite formation was the main route of metabolism in vitro, including a direct acyl-glucuronide observed in all species and a N-glucuronide in human.

Plasma clearance after single intravenous administration was found to be low to moderate in mouse, rat and dog corresponding to 37%, 5% and 1.2% of hepatic blood flow, respectively. The terminal plasma elimination half-life was long in mice and rats, and very long in dogs.

In vitro, amcenestrant showed very high intrinsic clearance using cryopreserved human. The biotransformation of amcenestrant was shown to be mainly non-cytochrome P450 (CYP) dependent (around 80% of clearance involve UDP-glucuronosyltransferase [UGT] 1A1 and 1A4) leading to direct glucuro-conjugation of amcenestrant. CYP2C8 and CYP3A are involved in amcenestrant oxidative metabolism. Therefore, there is a potential risk of interaction identified with UGTs, CYP2C8 and/or CYP3A inhibitors and inducers.

Based on in vitro data, there is no risk of inhibition of metabolizing enzymes by amcenestrant at clinically relevant concentrations. Amcenestrant showed in vitro a potential for induction on CYP2B6, CYP3A4, CYP2Cs, and UGT1A1 and 1A4. In vitro, amcenestrant was shown to be an potential inhibitor of P-gp and BCRP at absorption level, and of OATP1B1/B3 at systemic level.

4.4 RATIONALE FOR THE STUDY

TED14856 is an open-label, non-comparative, Phase 1/2 study which goals are to evaluate the safety profile, the efficacy, the pharmacokinetics (PK), and the PD of escalating doses of amcenestrant administered as a monotherapy, then in combination with the approved doses of palbociclib or other anti-cancer agents (alpelisib, everolimus and abemaciclib).

4.4.1 Arm #1

4.4.1.1 Part A (Dose Escalation, Monotherapy amcenestrant)

To assess the incidence rate of dose-limiting toxicity (DLT) and to determine the maximum tolerated dose (MTD) as well as the recommended dose of amcenestrant administered as monotherapy to postmenopausal women with advanced ER-positive and HER2-negative breast cancer.

The proposed starting dose and dose escalation scheme in the clinic is based on the results of the 4-week Good Laboratory Practice (GLP) toxicity studies conducted in two species dogs (females and males) and rat (females and males). The HNSTD was identified in the female dog at 30 mg/kg/day. The HNSTD or STD10 was not identified in the rat. Therefore, the starting dose was calculated based on the HNSTD in female dog as this was the most sensitive species in the GLP toxicity studies. The dose of 30 mg/kg/day in the dog corresponds to a dose of 160 mg/day in human and is the maximum allowable starting dose in patients according to International Conference on Harmonization guidelines in oncology patients (29).

In parallel to the toxicity studies, PK/PD correlations based on in vivo studies in mice and physiologically-based PK modelling prediction in human allowed to predict potential dose that inhibits the target (ER) occupancy in humans (IHC on mice tumor). The results of this simulation anticipate a daily dose of 20 mg to significantly inhibit the target on an ^{18}F-FES-PET basis (at least 90%). Therefore, it is envisaged to start this first in human study at 20 mg once a day, and, depending on the results of the ^{18}F-FES-PET scans (% of inhibition of the target) obtained, to increase the dose until reaching at least 90% of inhibition in all patients. Due to the limited availability of the ^{18}F-FES-PET scan technology, Part A will only be conducted in certain selected sites in US and France.

In addition, a twice daily (BID) dosing regimen will be assessed. A BID administration will allow modification of the PK behavior of the drug by increasing C_{trough} and decreasing C_{max} for a same dose intensity as once-daily regimen. It is expected that this regimen will allow a better and more constant coverage for ER inhibition.

Together with the DLT assessment, PK after repeated administration and level of inhibition of target occupancy measured by ^{18}F-FES-PET imaging (at baseline and during treatment) will also be taken into account for the decision to expand the study to Parts B and C.

4.4.1.2 Part B (Dose Expansion, Monotherapy amcenestrant)

When the dose escalation phase ends, a preliminary RD for Phase 2 will be proposed by the Study Committee for an expansion cohort (Part B), primarily based on safety, PD, and PK data. The primary endpoint will be the objective response rate (ORR) according to response evaluation criteria in solid tumors (RECIST v1.1) in postmenopausal advanced breast cancer patients. Testing on ESR1 mutation status will be done as part of the general characterization of the tumor. Exploring the activity of amcenestrant in ESR1 mutated patients may be of interest as when patients relapsed after AI therapy (but not after tamoxifen) ESR1 mutations is observed in 25% to 39% of women (30). Patients with ESR1 mutation had significantly improved PFS after taking fulvestrant monotherapy compared with exemestane (hazard ratio [HR]=0.52) (31) and after taking fulvestrant combined with palbociclib versus fulvestrant alone (HR=0.43) (13). In addition, an effort will be made to collect fresh biopsy of primary tumor or any metastatic site to evaluate the ER protein level by IHC and evaluate the ER degradation by comparing ER protein level determined by IHC in the most recently collected tumor.

The Part B expansion cohort will include approximately 78 patients. An interim analysis will be performed after 45 patients are treated in order to assess the efficacy: it is expected to have at least 5 patients with response (complete response [CR] or partial response [PR]); other parameters should also have to be taken into consideration such as the duration of response, clinical benefit rate (CBR, CR+PR+stable disease [SD] ≥24 weeks), the percentage of patients with SD, and the duration of SD.

If results in Part A with the BID dosing regimen are of interest in terms of safety, PK, exposure, preliminary efficacy and any other relevant information such as data from patients treated with the QD regimen, and warrants further investigation, a BID regimen could be tested in an additional expansion subpart with approximately 56 patients. In that case, an interim analysis will be performed after 29 patients are treated in order to assess the efficacy: it is expected to have at least 3 patients with response (complete response [CR] or partial response [PR]); other parameters should also have to be taken into consideration such as the duration of response, clinical benefit rate (CBR, CR + PR + stable disease [SD] ≥24 weeks), the percentage of patients with SD, and the duration of SD.

4.4.2 Arm #2

4.4.2.1 Part C (Dose Escalation, Combination with palbociclib)

Three recent studies in ER-positive postmenopausal breast cancer patients showed about 50% improvement on PFS with the combination of palbociclib, a CDK4/6 inhibitor, with hormone therapy versus hormone therapy alone. The phase 2 study PALOMA-1 (n=165 women) (12), and the confirmatory Phase 3 study PALOMA-2 (n=666 women) (32) assessed letrozole + palbociclib versus letrozole alone (or letrozole+placebo, respectively) in first line treatment achieving a PFS of 20.2 months with combination versus 10.2 months (HR=0.49; p=0.0004) and of 24.8 months with combination versus 14.5 months (HR=0.58; p <0.000001), respectively. The patient population was postmenopausal women with ER+, HER- advanced breast cancer and no prior systemic therapy.

The Phase 3 study PALOMA-3 (n=521 women) evaluated fulvestrant+palbociclib (patients with HR+, HER- metastatic breast cancer, progressive disease after endocrine therapy, and ≤1 chemotherapy for advanced breast cancer) versus fulvestrant+placebo achieving a PFS of 9.5 months with combination versus 4.6 months (HR=0.46; p <0.0001) (13).

Palbociclib is indicated for the treatment of ER-positive, HER2-negative advanced or metastatic breast cancer in combination with letrozole as initial endocrine based therapy in postmenopausal women, or with fulvestrant in women with disease progression following endocrine therapy.

The combination of amcenestrant with palbociclib in this study aims to assess the incidence rate of DLT and to determine the MTD as well as the RD of amcenestrant in combination with the recommended standard dosage of palbociclib administered to postmenopausal women with ER-positive and HER2-negative advanced breast cancer. It is intended to test 2 doses of amcenestrant QD (1 dose below amcenestrant RD and amcenestrant RD) with 1 fixed dose of palbociclib. Additionally, a BID regimen could be explored. Mutation profiling of circulating free DNA (cfDNA) will be determined at baseline and end of treatment (EOT) in order to explore a possible link between lack of response and the presence of specific tumor mutation.

Based on amcenestrant PK predictions in human, the risk of interaction of amcenestrant over the dose range planned (20 to 600 mg) on the PK of palbociclib at the RD (125 mg) is unlikely. In addition the PK of palbociclib in combination with amcenestrant will be characterized in this part of the study. Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans, consequently low or no risk of interaction of palbociclib on PK of amcenestrant is predicted. The first dose of amcenestrant will be one dose level below RD for monotherapy, and PK of amcenestrant in combination with palbociclib will be characterized in this part of the study. Due to the limited sample size, Part C will be conducted in the same sites which enrolled patients in Part A.

4.4.2.2 Part D (Dose Expansion, Combination with palbociclib)

When dose escalation of the combination phase in Part C ends, at least one dose for the expansion cohort (Part D) will be proposed by the Study Committee. More than 1 DL may be selected to be evaluated in this cohort. Approximately 28 patients will be treated at each selected dose from

Part C with approximately 56 patients enrolled if 2 dose levels are selected. Intra-patient dose escalation or re-escalation of any study drug is not allowed. The Study Committee will review the preliminary data (eg, safety, efficacy and PK), of each selected RD.

4.4.3 Arm #3

4.4.3.1 Part F (Safety Run-In Phase with alpelisib)

Amcenestrant 200 mg QD dose level will be assessed in combination with alpelisib at a fixed (standard) dose of 300 mg per alpelisib label according to incidence of DLTs and PK results. Additional dose levels of amcenestrant (eg, 300 mg QD, or 400 mg QD, or 100 mg BID, or 200 mg BID etc.) with alpelisib could be explored if needed based on the safety and PK results from the 200 mg dose level testing with 300 mg alpelisib. Lower dose of alpelisib (eg, 250 mg or 200 mg) could be explored from Cycle 1 Day 1 based on PK results and safety profile from the initial combination of amcenestrant 200 mg and alpelisib 300 mg on the first 3 to 6 patients in Part F.

A Phase 1b study conducted in 87 women with the combination of alpelisib and fulvestrant (sharing the same mechanism of action as amcenestrant) showed a manageable safety profile and suggested that the combination could have greater clinical activity in *PIK3CA*-mutated breast cancer compared to patients with *PIK3CA* wild-type tumors.

This was confirmed in a Phase 3 randomized and placebo-controlled SOLAR-1 study (16). In this study, patients with HR-positive, HER2-negative advanced or metastatic breast cancer who had experienced disease recurrence or progression following the use of an aromatase inhibitor were stratified by the presence or absence of a *PIK3CA* mutation and randomized to receive alpelisib with fulvestrant or placebo with fulvestrant. To note, only 20 of the 341 mutated patients had prior exposure to CDK4/6 inhibitors. The prespecified primary endpoint of SOLAR-1 was locally assessed progression-free survival in the cohort with *PIK3CA*-mutated breast cancer. In this cohort the PFS was 11.0 months in the alpelisib with fulvestrant group compared to 5.7 months in the placebo with fulvestrant group and this difference was highly statistically significant (hazard ratio for progression or death, 0.65; 95% CI, 0.50 to 0.85; P<0.001). Regarding disease response rate, among patients with measurable disease in the cohort with *PIK3CA*-mutated cancer the overall response rate was 35.7% in the alpelisib with fulvestrant group compared to 16.2% in the placebo with fulvestrant group.

Regarding toxicity and tolerance, the most frequent grade 3-4 adverse events in SOLAR-1 among the alpelisib with fulvestrant group were hyperglycemia (36.6%), rash (9.9%) and diarrhea (6.7%). A significant proportion of patients (25%) discontinued alpelisib due to adverse events, most commonly hyperglycemia (6.3%) and rash (3.2%). Dose reductions of alpelisib were permitted in SOLAR-1 with starting dose of 300 mg daily and reductions to 250 mg then 200 mg. The median relative dose intensity of alpelisib was 82.7% with dose reductions occurring in 63.9% of patients and dose interruptions in 74% of patients. In cohort A of the BYLieve study (17), 127 patients who had received a CDKi with an AI as immediate prior therapy were treated with alpelisib and fulvestrant. In this cohort, the most frequent grade 3-4 adverse were hyperglycemia (28.3%), rash (9.4%) and diarrhea (5.5%). Of note, 20.5% of these patients discontinued alpelisib due to adverse events, compared to 25% of patients in SOLAR-1, and there

were also fewer discontinuations related to hyperglycemia in BYLieve (33) compared to SOLAR-1 (1.6% and 6.3%, respectively).

Based on the PK properties of both drugs, amcenestrant could potentially increase alpelisib exposure through BCRP inhibition. Conversely, due to the potential induction effect of alpelisib on metabolizing enzymes (CYP2B6 and CYP2C9), alpelisib could decrease amcenestrant exposure (since CYP2Cs inducers may also induce the UGTs which is the main metabolic pathway for amcenestrant). Considering this uncertain risk of drug-drug interaction, PK of amcenestrant and alpelisib will be assessed in the safety run-in and expansion study parts.

4.4.3.2 Part G (Dose Expansion, Combination with alpelisib)

After the completion of the safety run-in (Part F), a recommended dose for Phase 2 will be proposed/confirmed by the Study Committee for an expansion cohort (Part G), primarily based on safety, PD, and PK data in Part F. Approximately 34 patients will be treated at the confirmed dose from Part F. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

The primary endpoint will be safety and tolerability per type, frequency, severity, relationship to study therapy and seriousness of adverse events (AE) or laboratory abnormalities according to NCI-CTCAE v4.03.

4.4.4 Arm #4

4.4.4.1 Part H (Dose Escalation with everolimus)

Amcenestrant 200 mg QD dose level will be assessed in combination with everolimus two dose levels: 5 mg QD and 10 mg QD based on the incidence of DLT(s) and PK results. Additional dose levels of amcenestrant (eg, 300 mg QD, or 400 mg QD, or 100 mg BID, or 200 mg BID etc.) with everolimus could also be explored if needed, based on the safety and PK results from this dose escalation study.

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP (34). Therefore, absorption and further elimination of everolimus may be influenced by amcenestrant which is a moderate CYP3A inducer and PgP inhibitor. In vitro, everolimus was reported as a potential UGT1A1 inhibitor (34), which may influence elimination of amcenestrant, mainly metabolized by UGT.

Pharmacokinetic assessment of both amcenestrant and everolimus will be conducted during dose escalation to anticipate any major interaction.

The BOLERO-2 study (14), which was conducted on 724 patients with HR+ advanced breast cancer who had recurrence or progression while on previous adjuvant treatment with Aromatase Inhibitor (letrozole or anastrozole) or other hormonal therapy (tamoxifen or fulvestrant) or chemotherapy, showed that the addition of everolimus to exemestane significantly improved progression-free survival, with observed medians of 11 months versus 4.1 months exemestane single agent.

4.4.4.2 Part I (Dose Expansion, Combination with everolimus)

After the completion of dose escalation study (Part H), based on safety, PK and preliminary antitumor activity data, RD of everolimus for the combination therapy will be proposed by Study Committee for expansion cohort (Part I); approximately 12 patients will be treated at the RD from Part H selected by the Study Committee. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

The primary endpoint will be safety and tolerability: type, frequency, severity, relationship to study therapy and seriousness of adverse events (AE) or laboratory abnormalities according to NCI-CTCAE v4.03.

4.4.5 Arm #5

4.4.5.1 Part J (Dose Escalation Phase with abemaciclib)

Amcenestrant 200 mg QD dose level will be assessed in combination with abemaciclib two dose levels: 100 mg BID and 150 mg BID based on the incidence of DLT(s) and PK results. Additional dose levels of amcenestrant (eg, 300 mg QD, or 400 mg QD, or 100 mg BID, or 200 mg BID etc.) with abemaciclib could also be explored if needed based on the safety and PK results from this dose escalation study.

The MONARCH 1 (35) study demonstrated that abemaciclib administered as a single agent on a continuous schedule had anti-tumor activity and manageable toxicities in patients with HR+/HER2- metastatic breast cancer who had previously progressed on or after endocrine therapy, and received 1-2 lines of chemotherapy in the metastatic setting. This was confirmed in the nextMONARCH (36) study that was conducted in the CDK4/6-naive patients who were also heavily pretreated.

In the MONARCH 2 (37), Phase 3 study, treatment with abemaciclib plus fulvestrant resulted in a statistically significant and clinically meaningful median OS improvement of 9.3 months for patients with HR+, HER2- advanced breast cancer who progressed after prior endocrine therapy regardless of menopausal status.

In the MONARCH 3 (38), Phase 3 study, treatment with abemaciclib plus letrozole resulted in a significantly longer median PFS than the placebo Arm (28.18 vs. 14.76 months; hazard ratio [95% confidence interval],0.540 [0.418–0.698]; p = .000002).

Abemaciclib is a primarily metabolized by CYP3A to several metabolites including three equipotent metabolites to abemaciclib (M2, M18 and M20). Elimination of abemaciclib, and possibly its metabolites, may be influenced by amcenestrant which is a potential CYP3A inducer. In addition, abemaciclib is a substrate of PgP and BCRP and its absorption may be influenced by amcenestrant which is a potential PgP inhibitor/inducer and BCRP inhibitor. It is not anticipated that abemaciclib will influence pharmacokinetics of amcenestrant. Pharmacokinetic assessment of both amcenestrant and abemaciclib will be conducted during dose escalation phase to anticipate any major interaction

4.4.5.2 Part K (Dose Expansion, Combination with abemaciclib)

After the completion of dose escalation study (Part J), a recommended dose of abemaciclib will be proposed for Phase 2 by the Study Committee for an expansion cohort (Part K), primarily based on safety, PD, and PK data in Part J. Approximately 20 patients will be treated at the confirmed dose from Part J. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

The primary endpoint will be safety and tolerability: type, frequency, severity, relationship to study therapy and seriousness of adverse events (AE) or laboratory abnormalities according to NCI-CTCAE v4.03.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVES

DOSE ESCALATION:

Monotherapy Arm #1 - Part A (amcenestrant monotherapy); Combination Arm #2 - Part C (amcenestrant in combination with palbociclib); Combination Arm #4 - Part H (combination of amcenestrant with everolimus); Combination Arm #5 - Part J (combination of amcenestrant with abemaciclib)

- To assess the incidence rate of DLT and to determine the MTD as well as the RD of amcenestrant administered as monotherapy (Part A), then in combination with palbociclib (Part C), in postmenopausal women with ER-positive and HER2-negative advanced breast cancer.
- To assess the incidence rate of dose-limiting toxicity (DLT) and determine the recommended dose (RD) of everolimus (part H) or abemaciclib (part J) administered in combination with the selected amcenestrant dose for the combination therapy

SAFETY RUN-IN Phase:

Combination Arm #3 - Part F amcenestrant in combination with alpelisib)

- To confirm the RD (Recommended Dose) of amcenestrant in combination with alpelisib in postmenopausal women with ER positive, HER2 negative and *PIK3CA*-mutated advanced breast cancer.

DOSE EXPANSION:

Monotherapy Arm #1 - Part B (amcenestrant monotherapy)

- To assess the antitumor activity using ORR according to RECIST v1.1 determined by an Independent Central Review (ICR) at the amcenestrant RD administered as monotherapy in postmenopausal women with ER-positive and HER2-negative advanced breast cancer.

Combination Arm #2 - Part D (amcenestrant in combination with palbociclib); Combination Arm #3 – Part G (combination of amcenestrant with alpelisib); Combination Arm #4 – Part I (combination of amcenestrant with everolimus); Combination Arm #5 – Part K (combination of amcenestrant with abemaciclib)

- To characterize the overall safety profile of amcenestrant administered in combination with palbociclib (Part D), in combination with alpelisib (Part G), in combination with everolimus (Part H), and in combination with abemaciclib (Part K)

5.2 SECONDARY OBJECTIVES

- To characterize the overall safety profiles of amcenestrant administered as monotherapy (Arm #1 Parts A and B), in combination with palbociclib (Arm #2 Part C), and in combination with alpelisib (Arm #3 Part F), everolimus (Arm #4 Part H) and abemaciclib (Arm #5 Part J).

- To characterize the PK profile of amcenestrant administered as monotherapy (Arm#1), or in combination in each study Arms, as well as the PK profile of palbociclib, alpelisib, everolimus and abemaciclib in the appropriate treatment arm.
- To evaluate the antitumor activity using **ORR** according to RECIST v1.1 of amcenestrant administered as monotherapy (Arm #1 Part A), in combination with palbociclib (Arm #2 Parts C and D), in combination with alpelisib (Arm #3 Part F and G), in combination with everolimus (Arm #4 Parts H and I), and in combination with abemaciclib (Arm #5 Parts J and K),the clinical benefit rate (**CBR**) defined as complete response [CR], partial response [PR] and stable disease [SD] ≥24 weeks, and progression-free survival (**PFS**) in each treatment arm.
- To evaluate the ORR and CBR (CR, PR and SD ≥24 weeks) in dose expansion of each study treatment arm according to the ESR1 gene mutational status (mutant and wild type) at baseline and during treatment.
- To evaluate the time to first response (CR or PR) in dose expansion of each study treatment arm.
- To evaluate residual ER availability with PET scan ^{18}F-FES uptake with increasing doses of amcenestrant (Arm #1 Part A).
- To assess the food effect on PK of amcenestrant (Arm #1 Part A).
- To assess potential induction/inhibition effect of amcenestrant on cytochrome P450 (CYP) 3A using 4b-OH cholesterol (ie, full PK sampling for Arm #1 Parts A and B, Arm#5 Parts J and K).

5.3 EXPLORATORY OBJECTIVES

- To evaluate PK/PD relationships.
- To evaluate target engagement: confirm the ER degradation with re-biopsy of the tumor at recommended dose in Arms #1 (Part B), #3 (Parts F,G), #4 (Parts H,I), and #5 (Parts J, K).
- To evaluate other breast cancer biomarkers in tumor over time such as Ki67, Bcl-2, PgR, ER and tumor gene expression profiles in Arms #1 (Part A, B), #3 (Parts F, G), #4 (Parts H, I), and #5 (Parts J, K). In Arm #5 (Parts J, K), Cyclin D1 protein expression will be evaluated too, at baseline and over time. Results will be correlated with patients' clinical parameters.
- To assess the extent of metastases with FDG PET/CT during dose escalation (Arm #1 Part A BID).
- To evaluate change of cfDNA alterations from screening to progression of disease during Arm #1 (Part B), #2, #3, #4, and #5. The percentage of patients with cfDNA alterations will be provided over time to characterize the biological evolution of the disease in each patient. The association of these alterations with clinical outcomes will also be provided.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is an open-label, non-comparative, dose escalation and dose expansion, safety, efficacy, PK, and PD evaluation study of amcenestrant administered orally as monotherapy (Parts A and B) and in the following combinations: with palbociclib (Parts C and D), alpelisib (Parts F and G), everolimus (Parts H and I) and abemaciclib (Parts J and K). Amcenestrant is given daily to postmenopausal women with ER-positive advanced breast cancer.

The study will be performed in 10 parts (5 Arms): the escalation phase with amcenestrant as monotherapy (Arm #1 Part A), an expansion phase with amcenestrant as monotherapy (Arm #1 Part B), an escalation phase with amcenestrant in combination with palbociclib (Arm #2 Part C), an expansion phase with amcenestrant in combination with palbociclib (Arm #2 Part D), safety run-in phase of amcenestrant with alpelisib (Arm #3 Part F), escalation phase with amcenestrant in combination with everolimus (Arm #4 Part H) and abemaciclib (Arm #5 Part J), and an expansion phase with amcenestrant in combination with alpelisib (Arm #3 Part G), everolimus (Arm #4 Part I) or abemaciclib (Arm #5 Part K).

Enrollment of patients in dose expansion Arms #1, #2, #3, #4, and #5 (Parts B, D, G, I and K) will be initiated after completion of dose escalation and safety run-in in Parts A, C, F, H and J, and identification of MTD/RD, and can be conducted in parallel. Patients' entry criteria in Parts B, D, G, I and K are slightly different with regards to prior anticancer therapy. Patients who are eligible to participate in other study parts, will not be able to participate in Parts F and G if they do not meet an additional inclusion criterion for these two study parts (F and G), ie, to have positive *PIK3CA* mutational status.

6.2 STARTING DOSE AND DOSE ESCALATION DESIGN

The rationale for selecting the starting dose is described in Section 4.

6.2.1 Starting dose and dose levels

Arm #1

Part A (monotherapy)

Dose escalation will be initiated with a QD schedule with a starting dose of 20 mg/day.

Dose escalation is expected to proceed according to Table 2. Intra-patient dose escalation or re-escalation will not be permitted.

Table 2 - Part A dose escalation

Dose level (DL)[a]	Dose of amcenestrant (mg)
DL(-1) QD	*10 once daily*
DL1 QD	20 once daily
DL1bis QD	*50 once daily*
DL2 QD	100 once daily
DL2bis QD	*150 once daily*
DL3 QD	200 once daily
DL4 QD	400 once daily
DL4bis BID[b]	200 twice daily
DL5 QD	600 once daily
DL5bis BID[b]	300 twice daily

a Additional intermediate or higher dose levels could be tested, after agreement between Sponsor and Investigators (Study Committee).
b A BID schedule of administration may be added during the study, the starting dose will be a DL of the same dose intensity as the highest cleared DL with QD Schedule. Other schedules of administration may be added during the study.

The BID dosing regimen will be explored in 6 DLT-evaluable patients at the dose level providing the same dose intensity as the highest cleared QD dose level (600 mg): 300 mg taken two times a day 12 hours apart (ie, 2 x 300 mg) ±1 hour (DL5bis BID). Other doses such as 100 mg and/or 200 mg taken two times a day 12 hours apart could also be explored if needed. In that case, 6 DLT-evaluable patients will be enrolled at each of these dose levels.

Arm #2 – amcenestrant in combination with palbociclib

Part C (combination)

Enrolment in the Part C dose escalation phase can be initiated once the amcenestrant RD monotherapy has been determined at the end of Part A. Dose escalation is expected to proceed according to Table 3. The starting dose of amcenestrant will be one dose level below the RD as monotherapy. Palbociclib will be given at the recommended standard dosage of 125 mg orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

Table 3 - Amcenestrant dose levels in Part C

Dose levels (DL)[a]	Amcenestrant	Palbociclib[b]
DL1 QD	DL RD(A-QD)-1	125 mg
DL2 QD	RD(A-QD)	125 mg
DL3 BID	RD(A-BID)	125 mg

a Lower dose, intermediate dose levels and a BID dose regimen can be tested after agreement between Sponsor and Investigators (Study Committee)
b Oral route once daily with food for 21 days followed by 7 days off therapy to comprise a complete cycle of 28 days. Lower dose (eg, 100 mg, 75 mg) can be proposed depending on tolerance

Arm #3 amcenestrant in combination with alpelisib

Part F

In Part F, safety run-in will be explored for amcenestrant given at one dose level below the RD as monotherapy (ie, 200 mg QD) and alpelisib given at the recommended standard dosage of 300 mg orally once daily for a complete cycle of 28 days (except in Cycle 1 where alpelisib will be taken alone for 3 days prior to amcenestrant administration [can be taken for 3 days in a 7 day window], followed by amcenestrant administration in combination with alpelisib for 25 days). An additional BID dose could be tested in Part F based on factors including safety profile and PK and guided by the Study Committee's recommendations.

Table 4 - Amcenestrant and alpelisib dose levels in Part F[a]

Dose levels (DL)[a]	Amcenestrant	Alpelisib (Standard dose)[b]	Alpelisib (reduced dose)[c]
DL1 QD	200 mg	300 mg	
DL2 QD	200 mg		250 mg
DL3 QD	200 mg		200 mg

a In Part F (and G), Cycle 1 is defined as a 28-day cycle with 3 days of pretreatment with alpelisib single-agent for PK assessment followed by a 25-day treatment cycle with amcenestrant and alpelisib. Following cycles will also continue to be 28 days.

a Lower or higher doses QD and a BID dose regimen can be tested after agreement between Sponsor and Investigators (Study Committee)

b Oral route, once daily with food.

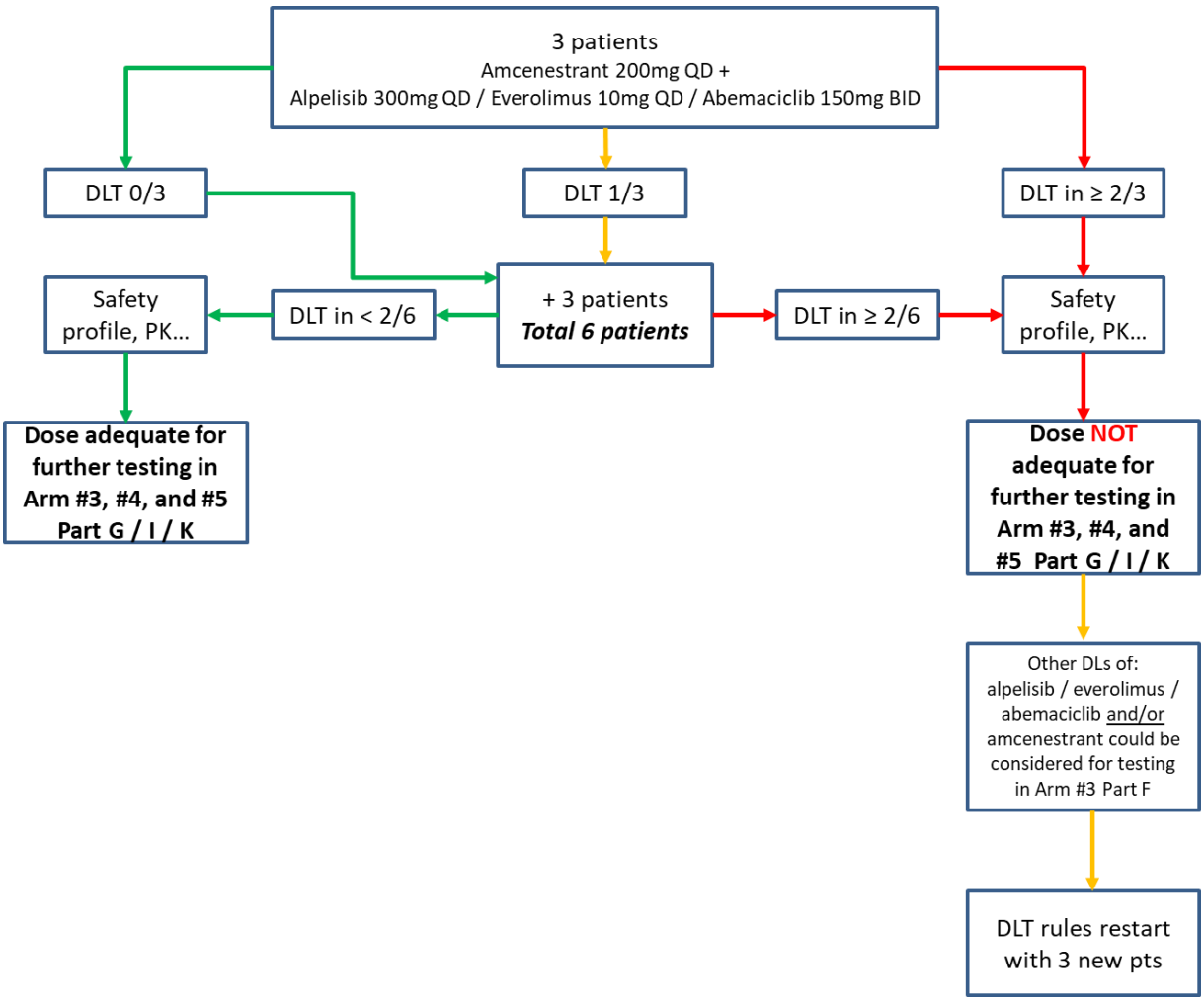
c Lower dose (eg, 250 mg, 200 mg) can be proposed depending on tolerance

Up to 6 DLT-evaluable patients could be treated at the already established amcenestrant dose of 200 mg when given in combination with other drugs, in order to confirm this dose when administered in combination with alpelisib. Lower dose levels of alpelisib and/or other dose levels of amcenestrant could be considered for testing in Part F if this established dose is not confirmed.

A decision to continue to dose expansion study part (Part G) will be based on DLTs observed for at least 1 cycle duration of all evaluable patients, and PK results from Part F combination. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

1. If none or one of the first 3 evaluable patients experiences DLT(s) during Cycle 1, the cohort will be expanded to include an additional 3 patients for a total of 6 patients.
    a) In the second set of 3 patients (ie, 6 patients altogether), if none or one DLT is experienced among the 6 patients (ie, 0/6 or 1/6), the doses of the combination are adequate for further testing in Part G.
    b) In the second set of 3 patients (ie, 6 patients altogether), if two or more DLTs are experienced among the 6 patients (ie, ≥2/6), the doses of the combination are NOT adequate for further testing in Part G. In this case, other dose levels of alpelisib and/or amcenestrant could be considered in Part F, or Part F can be stopped.
2. If 2 or more of the first 3 evaluable patients experience DLT(s), lower dose of alpelisib dose and/or other dose levels of amcenestrant will be considered or a decision to stop Part F can be made.

Although the confirmation of amcenestrant dose when given in combination with alpelisib will be guided by safety evaluation during Cycle 1, cumulative or irreversible toxicities observed after subsequent administrations will also be considered for dose selection/confirmation decision (ie, expansion of a given dose level), as well as any relevant information such as PK and anti-tumor activity data that may need additional patients, upon recommendation from the Study Committee.



Arm #4 amcenestrant in combination with everolimus

Part H

Amcenestrant 200 mg QD dose level will be assessed in combination with everolimus two dose levels: 5 mg QD and 10 mg QD based on the incidence of DLT(s) and PK results. In this dose escalation part, additional dose levels of amcenestrant (eg, 300 mg QD, or 400 mg QD, or 100 mg BID, or 200 mg BID etc.) with everolimus could also be explored if needed, based on the safety and PK results of everolimus in this dose escalation study.

Based on the preliminary safety profile, PK and antitumor activity data, Study Committee will determine the recommended dose (RD) of everolimus in combination with amcenestrant 200 mg QD, and/or expand this combination to Part I, or not.

Table 5 - Amcenestrant and everolimus dose levels in Part H[a]

Dose levels (DL)	Amcenestrant[b]	Everolimus[c] (QD)
DL1 QD	200 mg	5 mg
DL2 QD	200 mg	10 mg[d]

a In Part H, Cycle 1 is defined as a 28-day treatment cycle of amcenestrant and everolimus. Following cycles will also continue to be 28 days.
b Lower or higher doses QD and BID dose regimen can be tested after agreement between Sponsor and Study Committee
c Oral route, once daily (QD) with food.
d Lower dose of everolimus, (5mg QOD (every other day) can be explored depending on tolerance

Arm #5 amcenestrant in combination with abemaciclib

Part J

Amcenestrant 200 mg QD dose level will be assessed in combination with abemaciclib two dose levels: 100 mg BID and 150 mg BID according to incidence of DLT(s) and PK results. Additional dose levels of amcenestrant (eg, 300 mg QD, or 400 mg QD, or 100 mg BID, or 200 mg BID etc.) with abemaciclib could be explored if needed based on the safety and PK results from this dose escalation study.

Based on the preliminary safety profile, PK and preliminary antitumor activity data, the Study Committee will determine the recommended dose (RD) of abemaciclib in combination with amcenestrant 200 mg QD, and/or expand this combination to Part K, or not.

Table 6 - Amcenestrant and abemaciclib dose levels in Part J[a]

Dose levels (DL)	Amcenestrant[b]	Abemaciclib[c] (BID)
DL1 QD	200 mg QD	100 mg BID[d]
DL2 QD	200 mg QD	150 mg BID

a In Part J, Cycle 1 is defined as a 28-day treatment cycle of amcenestrant and abemaciclib. Following cycles will also continue to be 28 days.
b Lower or higher doses QD and BID dose regimen can be tested after agreement between Sponsor and Study Committee
c Oral route, twice daily (BID) with food.
d Lower doses of abemaciclib, 50 mg BID can be used depending on tolerance

6.2.2 Dose Escalation Arms #1, #2, #4 and #5 (Parts A, C, H and J) and Safety Run-In Arm #3 (Part F) strategy

The dose escalation decision will be based on the DLTs observed during Cycle 1. Before escalating the amcenestrant dose to the next level, the safety profile, PK profile, and ^{18}F-FES-PET results (Part A only) will be reviewed by the Study Committee. Cumulative or irreversible toxicities observed after subsequent administrations should also be considered for the dose escalation and the dose selection decision, upon recommendation from the Study Committee.

The Study Committee role is described in Section 6.10.

The definition of DLTs is provided in Section 9.1.1.

The classical dose escalation will be followed based on safety and PD evaluation. The first patient treated at each new dose level will be followed for a minimum of 1 week prior to enrolling and treating 2 additional patients at this dose level.

The following events will determine the total number of patients registered per dose level during the classical phase:

- If none of the 3 patients experience a DLT, the next cohort starts 1 dose level higher.
- If 1 of the 3 patients experiences a DLT, up to 3 additional patients are treated at this dose level.
- If 2 or more patients experience a DLT, the maximum administered dose (MAD) is reached.

The above plan is summarized hereafter:

Table 7 - Classical dose escalation phase

DLT observed at Cycle 1, in the first 3 patients:	DLT observed in the whole cohort:
DLT in 0/3 → escalate to the next dose level	-
DLT in 1/3 → add 3 more patients at the same level	• 1 DLT/6 patients → escalate to the next level • 2 DLTs/6 patients → define MAD
DLT in ≥2/3 → no additional patients	Defines MAD

DLT = dose limiting toxicity; MAD = maximum administered dose; implementation of prophylactic/curative therapies when appropriate

In addition, ^{18}F-FES-PET scan results should be available for all DLT-evaluable patients in Part A and depending on results at DL1 and 2, intermediate dose levels could be explored. The following rules regarding ^{18}F-FES-PET scan findings and dose levels to be tested will apply:

- If all patients treated at DL1 have 100% of inhibition of the target as shown on ^{18}F-FES-PET scan, DL(-1) will be explored.
- If all patients treated at DL1 have >70% inhibition of the target as shown on ^{18}F-FES-PET scan results, DL1bis will be explored.
- If at least one patient at DL1 has inhibition of the target as shown on ^{18}F-FES-PET scan results, between 30% and 70%, dose escalation will continue as planned and DL2 will be explored.
- If at least one patient at DL1 has ≤30% inhibition of the target as shown on ^{18}F-FES-PET scan results, DL2bis will be explored.
- If all patients treated at DL2 have >85% inhibition of the target as shown on ^{18}F-FES-PET scan results, DL2bis will be explored.
- If at least one patient at DL2 has ≤85% inhibition of the target as shown on ^{18}F-FES-PET scan results, dose escalation will continue as planned and DL3 will be explored.

From the 2 dose levels DL1bis and DL2bis, the next dose levels (DL2 and DL3 etc. respectively) should not be skipped.

Considering the exploratory context of ^{18}F-FES-PET scan, this strategy can be revised and adapted depending on the results.

At subsequent dose levels (≥DL3), other intermediate dose levels may be tested based on safety, ^{18}F-FES-PET scan results (if all patients have >90% of inhibition of the target) and PK parameters, upon recommendation from the Study Committee.

In Arms #1, #2, #3, #4, and #5, (Parts A, C, F, H and J) the second and third patients of a given dose level can only be enrolled when the first patient has received a minimum of 1 week of study treatment without DLT. The enrollment at the next dose level may not proceed before at least 3 patients treated at the current dose level have been followed for the duration of at least the first cycle (ie, 28 days) and are evaluable for DLT assessment.

In Arms #3, #4, and #5 (Parts F, H and J), it is planned to enroll approximately up to 12 evaluable patients (depending on the study part): 3 initial patients at the established amcenestrant dose of 200 mg in combination with alpelisib, everolimus or abemaciclib and upon the DLT assessment, 3 additional patients may be enrolled at the same dose level (Section 6.2.1). When Cycle 1 of other 3 treated patients is completed, and all patients are evaluable for DLT, the Study Committee will review safety and PK data in order to confirm recommended doses (RD) dose expansion.

6.3 MAXIMUM ADMINISTERED DOSE/MAXIMUM TOLERATED DOSE

As a rule, the dose escalation will stop when the MAD is reached, MAD being defined as the dose at which ≥33% (4 patients out of up to 12) of evaluable patients have experienced a DLT at Cycle 1.

In Arm #1 Part A, the MTD is defined as the highest dose level at which no more than 1 patient of a maximum of 6 patients experiences a DLT. Usually, the MTD is one dose level below the MAD, or the highest dose tested if the MAD is not reached.

The RD for the expansion cohort will be primarily based on safety data. However, especially if the MTD cannot be determined in the absence of DLTs at the MAD in Part A, PK after repeated administration, PD and target engagement results (level of ER occupancy measured by ^{18}F-FES-PET imaging) as well as any other relevant information could support the determination of the RD to expand the study to Part B. The RD should potentially be at least 2 dose levels above the dose level showing >90% of inhibition of the target on ^{18}F-FES-PET scan at this dose level, unless there are DLTs at this dose, in which case the RD could be any dose where >90% inhibition was reached.

In Arm #2, #4, and #5 (Part C, H, and J), the MTD is 1 dose level below the MAD or the highest dose tested if MAD is not reached.

Although the dose escalation process is guided by the safety evaluation during Cycle 1 treatment, cumulative and irreversible toxicities observed after subsequent administrations will also be considered for the dose escalation and dose selection decisions (ie, smaller increases in dose, expansion of a given dose level, intermediate dose level), upon agreement between the participant institutions and the Sponsor. Therefore, MAD/MTD will be defined/decided by the Study Committee, considering overall safety profile at all cycles.

6.4 RETREATMENT OF PATIENTS

The patient must have recovered to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade ≤1 or to their baseline status before institution of the next cycle at the same dose level. In those cases of clear clinical benefit, a patient can continue the study treatment until disease progression, unacceptable toxicity, or patient's decision.

In case of DLT, study treatment may continue upon resolution of DLT or recovery to Grade ≤1 or to their baseline status.

6.5 DOSE DELAYS/MODIFICATIONS

If a dose of any study drug is vomited or omitted the patient should not take the dose later or 2 doses at the next planned dose and this information has to be recorded in the diary.

Intra-patient dose escalation or re-escalation of any study drug is not allowed.

Amcenestrant should be taken continuously in all study parts and dose omission is allowed only in case of severe toxicity and the reason should be documented in the electronic case report form (eCRF).

In all study parts, if amcenestrant treatment is omitted for 2 consecutive weeks without resolution of the toxicity to Grade ≤1, the patient will be permanently discontinued from the study treatment unless a clear benefit is observed and this will be discussed on a case by case basis with the Sponsor. If the study treatment can be resumed within 2 weeks, dose decrease to the lower planned or intermediate dose level will be allowed depending on the type of toxicity.

There should be no amcenestrant dose reduction or omission for Grade 1 toxicities.

Grade 2: In the event of Grade 2 toxicities that are possibly related to amcenestrant, investigators should use their discretion in deciding whether to continue treatment. Patients experiencing Grade 2 non-hematologic AEs that are not easily managed or corrected and are not tolerable to the patient, or AEs that are not acceptable in the Investigator's judgment, should have study treatment omission until the AE resolves to Grade ≤1 or baseline.

Grade ≥3: In the event of Grade ≥3 toxicities (or DLTs), further treatment should be omitted until the toxicity is resolved to Grade 1 or baseline. If amcenestrant is permanently discontinued, study treatment will be stopped, ie, palbociclib, alpelisib, everolimus, and abemaciclib in the combination cohorts will also be discontinued.

For combination study drugs, the recommended dose modifications for palbociclib, alpelisib, everolimus and abemaciclib in case of adverse reactions are listed in Table 8, Table 10 and Table 11.

Table 8 - Dose levels for palbociclib and alpelisib dose reduction

	Palbociclib Dose	Alpelisib Dose
Recommended/starting dose	125 mg/day	300 mg/day
First dose reduction	100 mg/day	250 mg/day
Second dose reduction	75 mg/day[a]	200 mg/day[a]

a If further dose reduction below 75 mg/day (palbociclib) or 200 mg/day (alpelisib) is required, palbociclib/alpelisib respectively, will be permanently discontinued

Table 9 - Dose levels for everolimus and abemaciclib dose reduction

	Everolimus Dose	Abemaciclib Dose
Starting dose	5 mg/day or 10 mg/day	100 mg/twice daily or 150 mg/twice daily
Dose reduction*	5 mg/every other day[a] or 5 mg/every day[a]	50 mg/twice daily[b] or 100 mg/twice daily[b]

a If further dose reduction below 5 mg/every day is needed, dose can be reduced to 5 mg/every other day; if additional dose reduction is needed (ie, below 5 mg/every other day), everolimus will be permanently discontinued.
b If further dose reduction of abemaciclib (below 50 mg twice a day) is needed, they will be permanently discontinued.

6.5.1 Arm #2 Parts C and D

Table 10 - Dose modification and management: hematologic toxicities

CTCAE Grade	Dose modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3	Day 1 of cycle: continue amcenestrant at the same dose, omit palboclib dosing, repeat complete blood count monitoring within 1 week (or as per Investigators' judgement). When recovered to Grade ≤2, restart palbociclib at the *same* dose. Days 8 and 15 of first 2 cycles: continue amcenestrant at the same dose, continue palbociclib at current dose to complete cycle. Repeat complete blood count on Day 22. Consider palbociclib dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia in subsequent cycles and maintain amcenestrant at the *same* dose.
Grade 3 and 4 neutropenia[a] with fever ≥38.5ºC and/or infection or Grade 4[b]	Day 1 of a cycle: continue amcenestrant at the same dose, omit palboclib dosing, repeat complete blood count monitoring within 1 week (or as per Investigators' judgement). When recovered to Grade ≤2, restart palbociclib at the *next lower dose.* Restart could be either within the current cycle if recovery occurs before D21 of the cycle (and administration is up to D21 of the cycle) or at D1 of the next planned cycle. Within a cycle: continue amcenestrant at the same dose, omit palboclib dosing if applicable (ie, within D1 to D21 period of a given cycle), repeat complete blood count monitoring within 1 week (or as per Investigators' judgement). When recovered to Grade ≤2, restart palbociclib at the same dose. Restart could be either within the current cycle if recovery occurs before Day 21 of the cycle (and administration is up to D21 of the cycle) or at D1 of the next planned cycle

Note: Table applies to all hematologic abnormalities except lymphopenia (unless associated with clinical events, eg, opportunistic infections).
a Absolute neutrophil count (ANC): Grade 1: ANC <LLN -1500/mm^3; Grade 2: ANC 1000 -<1500/mm^3; Grade 3: ANC 500 -<1000/mm^3;
b Grade 4: ANC 500/mm^3
Grading according to CTCAE 4.03.
CTCAE = Common Terminology Criteria for Adverse Events; LLN = lower limit of normal.

Table 11 - Dose modification and management: non-hematologic toxicities

CTCAE grade	Dose modifications
Grade 1 or 2	Continue amcenestrant and palbociclib as planned. No dose adjustment is required.
Grade ≥3 nonhematologic toxicity attributed to palbociclib (if persisting despite optimal medical treatment)	At any time: continue amcenestrant at the same dose, omit palboclib dosing, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, restart palbociclib at the *next lower dose.* Palbociclib should always be taken for 3 weeks regardless of the cycle.

CTCAE = Common Terminology Criteria for Adverse Events

In study Parts C or D, patients should be monitored for any new or worsening of respiratory symptoms and be advised to report such symptoms promptly. If patients show any signs or symptoms of suspecting interstitial lung disease (ILD)/Pneumonitis (eg, hypoxia, cough, dyspnea), treatment with palbociclib should immediately be omitted, and appropriate diagnosis testing should be initiated as well as appropriate treatment if judged necessary by the investigator. If patients are diagnosed with ILD/Pneumonitis, palbociclib should be prematurely or permanently discontinued (Table 12).

Table 12 - Dose modification and management - ILD/Pneumonitis

CTCAE Grade[a]	Dose Modifications
Grade 1 (asymptomatic or suspected pneumonitis) or Grade 2 (symptomatic new or worsening respiratory symptoms)	At any time: continue amcenestrant at the same dose and omit palbociclib if applicable (ie, within D1 to D21 period of a given cycle); evaluate the patient until pneumonitis is diagnosed when palbociclib must be prematurely permanently discontinued.
Grade 3 & 4 attributed to palbociclib	Any day of a cycle: continue amcenestrant at the same dose and permanently discontinue palbociclib

a Grading according to CTCAE 4.03.
CTCAE = Common Terminology Criteria for Adverse Events; LLN = lower limit of normal.

6.5.2 Arm #3 Dose modification in Parts F and G

For severe hypersensitivity, which is manifested by, but not limited to symptoms such as dyspnea, flushing, rash, fever, or tachycardia, alpelisib should be discontinued permanently. An appropriate treatment should be promptly initiated.

If a patient requires a dose omission of amcenestrant >14 days from the intended day of the next scheduled dose, the patient should be discontinued from the study treatment.

Table 13 - Dose modification for alpelisib

CTCAE Grade[a]	Dose Modifications
Severe cutaneous reactions (SJS, TEN, EM, DRESS)[b, c]	
Grade 3 and 4	Permanently discontinue both, amcenestrant and alpelisib treatments.
Rash[d]	
Grade 1 (<10% body surface area (BSA) with active skin toxicity[e]) and Grade 2 (10-30% BSA with active skin toxicity[e])	Continue amcenestrant and alpelisib as planned. No dose adjustment is required[f].
Grade 3 (>30% BSA with active skin toxicity[e])	Omit both, amcenestrant and alpelisib until symptoms recover to Grade ≤1; if symptoms recover to Grade ≤1, resume amcenestrant at the same dose level and alpelisib either at the same dose level for the first occurrence of rash, or at the next lower dose level in case of second occurrence[f].
Grade 4 (any % BSA associated with extensive superinfection, with IV antibiotics indicated: life-threatening consequences)	Permanently discontinue both amcenestrant and alpelisib treatments. Consult a dermatologist. Treatment may follow guidelines for Grade 3 with the exception of restart of alpelisib[f]. Additional measures may be taken as per local treatment guidance.
Hyperglycemia[g]	
Grade 1 (FPG >ULN-160 mg/dL or >ULN-8.9 mmol/L For patients with baseline values between >ULN – 140 mg/dL (ULN – 7.7 mmol/L) this applies only for values >140 mg/dL (7.7 mmol/L)	Continue amcenestrant and alpelisib as planned. No dose adjustment is required. Initiate or intensify oral anti-diabetic treatment[h], and remind patient on lifestyle changes[i].
Grade 2 (FPG>160-250 mg/dL or >8.9-13.9 mmol/L)	Continue amcenestrant and alpelisib as planned. No dose adjustment is required. Remind patient on lifestyle changes[i]. Initiate or intensify oral anti-diabetic treatment[h, j, k]. Repeat FPG within 24 hours, then twice a week until FPG resolves to ≤ Grade 1, and as clinically indicated. If FPG does not decreased to ≤160 mg/dL or 8.9 mmol/L within 21 days under appropriate anti-diabetic treatment, reduce alpelisib dose by 1 dose level, continue amcenestrant at the same dose and follow FPG value specific recommendations: continue with anti-diabetic treatment and check FPG levels at least weekly for 8 weeks, then continue checking at least every 2 weeks; alert treating physician if FPG >250 mg/dL.
Grade 3 (FPG>250-500 mg/dL or >13.9-27.8 mmol/L)	Continue amcenestrant at the same dose level and omit alpelisib until symptoms recover to Grade ≤1. Repeat FPG within 24 hours, then twice a week until FPG resolves to ≤ Grade 1, and as clinically indicated. Initiate or intensify oral anti-diabetic treatment[h, j] and consider additional anti-diabetic medications (insulin) for 1-2 days until hyperglycemia improves. Administer intravenous hydration and consider appropriate treatment (eg, intervention for electrolyte/ketoacidosis/hyperosmolar disturbances). If FPG decreased to ≤160 mg/dL or 8.9 mmol/L within 3 to 5 days under appropriate anti-diabetic treatment, resume alpelisib at 1 lower dose level. A second and third oral hypoglycemic agent may be initiated concomitantly, if needed, in consultation with a diabetologist. Check FPG at least weekly for 8 weeks and then continue checking at least every 2 weeks; alert treating physician if FPG >250 mg/dL.

CTCAE Grade[a]	Dose Modifications
	If FPG does not decrease to ≤160 mg/dL or 8.9 mmol/L within 3 to 5 days while off of alpelisib and under appropriate anti-diabetic treatment (eg, with metformin), consultation with expertise in the treatment of hyperglycemia is recommended and do not resume alpelisib. If FPG does not decrease to ≤160 mg/dL or 8.9 mmol/L within 21 days following appropriate anti-diabetic treatment in cooperation with diabetologist and exclusion of confounding factors eg, urinary tract infection, prematurely discontinue alpelisib treatment and continue amcenestrant at the same dose.
Grade 4 (FPG >500 mg/dL or ≥27.8 mmol/L)	Continue amcenestrant at the same dose level and omit alpelisib until symptoms recover Grade ≤1. Re-check FPG within 24 hours and as clinically indicated. Initiate or intensify appropriate anti-diabetic treatment[h]; administer intravenous hydration and consider appropriate treatment (eg, intervention for electrolyte/ketoacidosis/hyperosmolar disturbances), re-check FPG within 24 hours. If FPG decreases to ≤500 mg/dL or 27.8 mmol/L, follow FPG value specific recommendations for Grade 3. If FPG is confirmed at >500 mg/dL or 27.8 mmol/L, prematurely discontinue alpelisib treatment.
ILD/Pneumonitis[l]	
Grade 1 (asymptomatic or suspected pneumonitis) or Grade 2 (symptomatic new or worsening respiratory symptoms)	Continue amcenestrant at the same dose and omit alpelisib; after ruling out infectious etiology and upon making a diagnosis of pneumonitis, prematurely discontinue alpelisib and promptly initiate appropriate treatment and supportive measures. If Pneumonitis is not diagnosed, restart alpelisib at the next lower dose when symptoms recover to the baseline level
Grade 3 or 4	Continue amcenestrant at the same dose and prematurely discontinue alpelisib treatment.
Diarrhea (frequent and watery bowel movements)	
Grade 1	Continue amcenestrant and alpelisib as planned. No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2	Continue amcenestrant at the same dose and omit alpelisib dose until symptoms recover to Grade ≤1, then resume alpelisib at the same dose level. In case of the second episode, omit alpelisib dose until resolved to ≤ Grade 1, then decrease one dose level. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3	Omit both, amcenestrant and alpelisib until symptoms recover to Grade ≤1; if symptoms recover to Grade ≤1, resume amcenestrant at the same dose and alpelisib at the next lower dose level. Initiate appropriate medical therapy and monitor as clinically indicated[m].
Grade 4	Permanently discontinue both, alpelisib and amcenestrant treatment. Manage according to local standard of care medical management as clinically indicated[m].
Isolated Total Bilirubin Elevation	
Grade 1 (>ULN - 1.5 x ULN)	Continue amcenestrant and alpelisib as planned. No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (>1.5 - 3.0 x ULN)	Omit both, amcenestrant and alpelisib doses until recovery to Grade ≤1 and resume both study drugs at the same dose if resolved in ≤14 days, or resume amcenestrant at the same dose and alpelisib at the next lower dose level if resolved in >14 days.
Grade 3 (>3.0 - 10.0 x ULN)	Omit both, amcenestrant and alpelisib dose until recovery to Grade ≤1, then resume amcenestrant at the same dose and alpelisib at the next lower dose level.
Grade 4 (>10.0 x ULN)	Permanently discontinue both, amcenestrant and alpelisib treatment.

CTCAE Grade[a]	Dose Modifications
Isolated ALT or AST Elevation	
Grade 1 (>ULN - 3.0 x ULN) & Grade 2 (>3.0 - 5.0 x ULN)	Continue amcenestrant and alpelisib as planned. No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3 (>5.0 - 20.0 x ULN)	Omit both, amcenestrant and alpelisib until recovery to Grade ≤1. Repeat LFTs within 2-3 days. If ALT or AST levels do not recover, monitor LFTs weekly (or more frequently, if clinically indicated) until recovery to Grade ≤1 or baseline. On recovery, restart amcenestrant at the same dose and alpelisib at the next lower dose. In case of the first recurrence of the same Grade 3 event, administer amcenestrant at the same dose and alpelisib at the next lower dose if restart is possible. If further dose reduction below 200 mg/day is needed, prematurely discontinue alpelisib. In case of the second recurrence of the same Grade 3 event, permanently discontinue both, amcenestrant and alpelisib.
Grade 4 (>20.0 x ULN)	Permanently discontinue both, amcenestrant and alpelisib treatment.
Asymptomatic Amylase and/or Lipase Elevation	
Grade 1 (>ULN - 1.5 x ULN) & Grade 2 (>1.5 - 2.0 x ULN)	Continue amcenestrant and alpelisib as planned. No dose adjustment is required.
Grade ≥3 (>2.0 x ULN)	Omit both, amcenestrant and alpelisib dose until resolved to Grade ≤1 or baseline; if resolved in ≤14 days, resume both study drugs at the same dose. If resolved in >14 days, resume amcenestrant at the same dose and alpelisib at the next lower dose level Note: In cases of isolated amylase elevations only, alpelisib dosing may be maintained provided amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. Monitor total amylase and continue to assess fractionated amylase[o]
Other toxicities[n, p, q]	
Grade 1 and 2	Continue amcenestrant and alpelisib as planned. No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3 attributed to alpelisib	Continue amcenestrant at the same dose and omit alpelisib dose until symptoms recover to Grade ≤1, then resume alpelisib at the next lower dose level. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 4 attributed to alpelisib	Permanently discontinue both, alpelisib and amcenestrant treatments[n]

a Grading according to CTCAE 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)

b Severe Cutaneous Reactions (SCR): Stevens-Johnson Syndrome [SJS], Erythema Multiforme [EM], Toxic epidermal necrolysis [TEN], and Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]. If signs or symptoms of (non) confirmed/diagnosed Severe Cutaneous Reactions are present, omit alpelisib and amcenestrant until symptoms recover to Grade ≤1; if symptoms recover to Grade ≤1, resume amcenestrant at the same dose level and permanently discontinue alpelisib. Consultation with dermatologist is mandated for SCR, DRESS and all serious cutaneous reactions that fulfil serious criteria for AE reporting.

c For all grades of severe cutaneous reaction, consider consultation with dermatologist.

d Please refer to Section 8.6 (Concomitant Medications) for premedication and treatment recommendations.

e "Active" skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered "active" any longer. A topical corticosteroid treatment can be reduced in these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy.

f Initiate (Grade 1 & 3) / intensify (Grade 2) topical corticosteroids 3-4 x daily (preferred compounds to use are triamcinolone or betamethasone for up to 28 days, as long as skin toxicity is active). If active rash is not resolved within 28 days of appropriate treatment, add low dose systemic corticosteroid (20-40 mg/d), such as prednisone 10 mg 3x daily. For patients with symptoms like burning and/or pruritus add a non-sedating antihistamine such as cetirizine once daily during daytime and a sedating antihistamine such as diphenhydramine once daily at night. If Grades 2 & 3 improve to ≤ Grade 1 within 10 days systemic corticosteroid may be discontinued. For Grade 3, antihistamine regimen should be continued for a minimum of 28 days after re-challenge with alpelisib. If rash/skin toxicity still active in up to 10% BSA (ie, Grade 1) after more than 14 days, continue oral corticosteroid for at least 48 hours upon re-challenge with alpelisib; if rash and/or pruritus do not reoccur within 48 hours after re-challenge with alpelisib, systemic corticosteroid may be discontinued.

g FPG/Blood Glucose/Grade levels reflect hyperglycemia grading according to CTCAE v.4.03.

h Initiate applicable anti-diabetic medications: 1) Metformin 500 mg orally once daily with dinner. If no gastrointestinal (GI) intolerance after several days, increase to 500 mg bid, with breakfast and dinner. If tolerated, increase to 500 mg with breakfast, and 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Titrate metformin to the MTD over a period of 3 weeks. 2) Alternatively, consider starting an SGLT2 inhibitor (Sodium-Glucose Transport Protein 2) alone or in combination with metformin, especially in patients at risk for developing severe hyperglycemia. Starting dose and titration should be in accordance with the local prescribing information and consistent with local practice. 3) Monitor FPG levels as clinically indicated and at least twice weekly for 8 weeks, then continue checking at least weekly until FPG is within baseline values.

i Alpelisib, like other PI3K inhibitors, may affect glucose homeostasis which could result in increases of plasma glucose and insulin resistance. Alpelisib induced hyperglycemia is generally manageable with adequate anti-diabetic treatment. Alpelisib induced hyperglycemia typically occurs within the first month of treatment. Patients with pre-diabetes (ie, FPG 100 – 125 mg/dL; 5.6 - 6.9 mmol/L) and those with an established diagnosis of type 2 diabetes mellitus should be monitored carefully, thus allowing an early detection and prompt management of increases in fasting glucose while on alpelisib. The treatment includes early administration of metformin or a sodium-glucose cotransporter 2 (SGLT2) inhibitor (alone or in combination with metformin). Fasting plasma glucose testing may be performed at site for rapid availability for safety evaluation and management guidance. Special attention should be paid to the risk of hypoglycemia in patients interrupting alpelisib treatment and concomitantly receiving insulin and/or sulfonylureas. Due to the short half-life of alpelisib, all glucose lowering medications should be discontinued when alpelisib is stopped. If metformin or an anti-diabetic agent is interrupted for radiologic assessments or another reason, then alternative hyperglycemia management should be considered for those days to ensure optimal hyperglycemia management. Consultation with a diabetologist or healthcare provider experienced in the management of hyperglycemia is highly recommended for better assessment and management of alpelisib-induced hyperglycemia.

j Exclude confounding factors like eg, urinary tract infection and consider consultation with a healthcare expert experienced in hyperglycemia management or a diabetologist.

k Additional oral anti-diabetic agents may be initiated, if needed (especially in patients at risk for developing severe hyperglycemia). If FPG levels are still rising on MTD of metformin or persistently >160 mg/dL (>8.9 mmol/L), add an SGLT2 inhibitor if available, eg, empagliflozin up to 25 mg (max. dose) with metformin or alternatively start an SGLT2 inhibitor alone or in combination with metformin.

l Symptoms of pneumonitis may include hypoxia, cough, dyspnea, interstitial infiltrates on radiologic exams (high resolution CT scan) broncho-alveolar lavage (BAL); biopsy should be considered if clinically appropriate. Infectious causes of interstitial lung disease should be ruled out (infectious, neoplastic, and other causes by means of appropriate investigation). The institutional practice for management of pneumonitis should be followed which generally includes treatment with high dose corticosteroids (antibiotic therapy should be administered concurrently if infectious causes are suspected). Consultation with a pulmonologist is highly recommended for any pneumonitis case during the study treatment.

m Electrolyte monitoring, administration of antiemetics and antidiarrheal medicinal products and/or fluid replacement and electrolyte supplements

n Omit both, amcenestrant and alpelisib dose for vomiting Grade ≥3 or nausea Grade 3 only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice).

o Grade 3 must be tested weekly (or more frequently if clinically indicated) until ≤ Grade 1 (or baseline). After dosing is resumed, continue to test weekly for one additional cycle. If no reoccurrence of ≥ Grade 2 event, continue monitoring every cycle. An exception to these follow-up guidelines will be made for cases of isolated amylase elevations in which amylase fractionation demonstrates that pancreatic amylase is ≤Grade 1. In such cases, total amylase and fractionated amylase should be monitored weekly (or more frequently if clinically indicated) for 4 weeks. If pancreatic amylase remains ≤ Grade 1, subsequent monitoring must be performed at least every 4 weeks (or more frequently if clinically indicated).

Patients who discontinue study treatment due to pancreatic toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ Grade 1 or stabilization occurs (no CTCAE v4.03 grade change over 4 weeks). If amylase and/or lipase elevations are accompanied by new or progressive unexplained abdominal symptoms such as severe pain or vomiting, omission of study treatment, then perform diagnostic procedures (eg, abdominal CT scan or ultrasound) to exclude pancreatic pathology.

p Toxicities excluding Hyperglycemia, Severe Cutaneous Reaction, Rash, Pneumonitis, and Diarrhea

q For Grade 2 and 3 pancreatitis, omit amcenestrant and alpelisib dose until recovery to Grade ≤1; resume amcenestrant at the same dose and alpelisib at the next lower dose level. Only one dose reduction is permitted. If toxicity reoccurs, permanently discontinue alpelisib treatment.

6.5.3 Arm #4 Dose modification in Parts H and I

Table 14 - Everolimus dose modification and management: hematologic toxicities

Adverse events	CTCAE Grade	Dose modification
Thrombocytopenia	Grade 1	Continue amcenestrant and everolimus as planned. No dose adjustment is required.
	Grade 2	Day 1 of the cycle: continue amcenestrant at the same dose, omit everolimus until improvement to Grade 0 or 1. Resume everolimus at the same dose.
	Grade 3 or 4	Days 8 and 15 of the first 2 cycles: continue amcenestrant at the same dose, omit everolimus until improvement to Grade 0 or1. Resume everolimus at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
Neutropenia[a]	Grade 1 or 2	Continue amcenestrant and everolimus as planned. No dose adjustment is required.
	Grade 3	Day 1 of the cycle: continue amcenestrant at the same dose, omit everolimus until improvement to Grade 0, 1, or 2. Resume everolimus at the same dose.
	Grade 4	Continue amcenestrant and permanently discontinue everolimus.
Febrile neutropenia[b]	Grade 3	Day 1 of the cycle: continue amcenestrant at the same dose, omit everolimus until improvement to Grade 0, 1, or 2, and no fever. Resume everolimus at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
	Grade 4	Continue amcenestrant and permanently discontinue everolimus.

a Absolute neutrophil count (ANC): Grade 1: ANC <LLN -1500/mm^3; Grade 2: ANC 1000 -<1500/mm^3; Grade 3: ANC 500 -<1000/mm^3
b Grade 4: ANC 500/mm3
Grading according to CTCAE 4.03.
CTCAE = Common Terminology Criteria for Adverse Events; LLN = lower limit of normal.

Table 15 - Everolimus Dose modification and management: non-hematologic toxicities

Adverse events	CTCAE Grade	Dose modification
Non-infectious pneumonitis	Grade 1	Continue amcenestrant and everolimus as planned. No dose adjustment is required.
	Grade 2	At any time: continue amcenestrant at the same dose, omit everolimus until improvement to Grade 0 or 1. Resume everolimus at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. Permanently discontinue if toxicity does not resolve or improve to Grade 1 within 4 weeks.
	Grade 3	At any time: continue amcenestrant at the same dose, omit everolimus until improvement to Grade 0 or 1. Resume everolimus at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. If toxicity reoccurs at Grade 3, permanently discontinue.
	Grade 4	Continue amcenestrant and permanently discontinue everolimus.

Adverse events	CTCAE Grade	Dose modification
Stomatitis[a]	Grade 1	Continue amcenestrant and everolimus as planned. No dose adjustment is required.
	Grade 2	At any time: continue amcenestrant at the same dose, omit everolimus until improvement to Grade 0 or 1. Resume everolimus at same dose. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
	Grade 3	At any time: continue amcenestrant at the same dose, omit everolimus until improvement to Grade 0 or 1. Resume everolimus at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
	Grade 4	Continue amcenestrant and permanently discontinue everolimus.
Metabolic events (eg, hyperglycemia, dyslipidemia)	Grade 1 or 2	Continue amcenestrant and everolimus as planned. No dose adjustment is required.
	Grade 3	At any time: continue amcenestrant at the same dose, omit everolimus until improvement to Grade 0, 1, or 2. Resume everolimus at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
	Grade 4	Continue amcenestrant and permanently discontinue everolimus.
Other non-hematologic toxicities	Grade 1	Continue amcenestrant and everolimus as planned. No dose adjustment is required.
	Grade 2 .	At any time: continue amcenestrant at the same dose, omit everolimus until improvement to Grade 0 or 1. Resume everolimus at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. If toxicity becomes intolerable, omit everolimus until improvement to Grade 0 or 1. Resume it at the same dose.
	Grade 3	At any time: omit amcenestrant and everolimus until improvement to Grade 0 or 1. Once recovered, resume amcenestrant at the same dose and consider resuming everolimus at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. If recurs at Grade 3, permanently discontinue.
	Grade 4	Continue amcenestrant if considered not related, otherwise permanently discontinue both amcenestrant and everolimus.

a As a preventative measure of Stomatitis, initiate dexamethasone alcohol-free mouthwash when starting treatment as per label instructions.

6.5.4 Arm #5 Dose modification in Parts J and K

Discontinue abemaciclib if patients are unable to tolerate 50 mg twice daily.

Table 16 - Abemaciclib Dose modification and management: hematologic toxicities[a]

CTCAE Grade	Dose modification
Grade 1 or 2	Continue amcenestrant and abemaciclib as planned. No dose modification is required.
Grade 3	At any time: continue amcenestrant at the same dose, omit abemaciclib until toxicity resolves to ≤Grade 2. Dose reduction is not required.
Grade 3 recurrent or Grade 4	At any time: continue amcenestrant at the same dose, omit abemaciclib until toxicity resolves to ≤Grade 2. Resume at the next lower dose

a If blood cell growth factors are required, omit abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume at the next lower dose unless already performed for the toxicity that led to the use of the growth factor. Growth factor use as per current treatment guidelines.

Table 17 - Abemaciclib Dose modification and management: non-hematologic toxicities

CTCAE Grade	Dose modification
Diarrhea[a]	
Grade 1	Continue amcenestrant and abemaciclib as planned. No dose modification is required.
Grade 2	At any time: continue amcenestrant at the same dose. If toxicity does not resolve within 24 hours to ≤ Grade 1, omit abemaciclib dose until resolution. No dose reduction is required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	At any time: continue amcenestrant at the same dose, omit abemaciclib dose until toxicity resolves to ≤ Grade 1. Resume at the next lower dose.
Grade 3	At any time: omit both, amcenestrant and abemaciclib until toxicity resolves to ≤Grade 1. Once resolved, resume amcenestrant at the same dose and abemaciclib at the next lower dose.
Grade 4 or hospitalization	Continue amcenestrant if considered not related, otherwise permanently discontinue both amcenestrant and abemaciclib.
Hepatoxicity[b]	
Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	Continue amcenestrant and abemaciclib as planned. No dose modification is required.
Persistent or Recurrent Grade 2, or Grade 3 (>5.020.0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	At any time: continue amcenestrant at the same dose, omit abemaciclib dose until toxicity resolves to baseline or Grade 1. Resume at the next lower dose.
Elevation in AST and/or ALT >3 x ULN WITH total bilirubin >2 x ULN, in the absence of cholestasis	At any time: omit amcenestrant until recovery to Grade ≤1. Repeat LFTs within 2-3 days. If ALT or AST levels do not recover, monitor LFTs weekly (or more frequently, if clinically indicated) until recovery to Grade ≤1 or baseline. On recovery, restart amcenestrant at the same dose and permanently discontinue abemaciclib.
Grade 4 (>20.0 x ULN)	Permanently discontinue both, amcenestrant and abemaciclib treatment.

CTCAE Grade	Dose modification
Other toxicities	
Grade 1 or 2	Continue amcenestrant and abemaciclib as planned. No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	At any time: continue amcenestrant at the same dose, omit abemaciclib dose until toxicity resolves to baseline or ≤Grade 1. Resume at the next lower dose.
Grade 3	At any time: continue omit both, amcenestrant at the same dose, omit and abemaciclib dose until toxicity resolves to ≤Grade 1. Once resolved, Resume both amcenestrant at the same dose and abemaciclib at the next lower dose.
Grade 4	Continue amcenestrant if considered not related, otherwise permanently discontinue both amcenestrant and abemaciclib.

a At the first sign of loose stools, start treatment with antidiarrheal agents and increase intake of oral fluids.

b Monitor ALT, AST, and serum bilirubin prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.

Avoid concomitant use of the strong CYP3A inhibitor ketoconazole. With concomitant use of other strong CYP3A inhibitors, in patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the abemaciclib dose to 100 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the abemaciclib dose to 50 mg twice daily. If a patient taking abemaciclib discontinues a strong CYP3A inhibitor, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor.

6.6 EXPANSION COHORTS TO CONFIRM THE MAXIMUM TOLERATED DOSE

In Arm #1 Part B, approximately 78 patients will be treated at the RD of amcenestrant in QD to collect safety, PK, and efficacy data. If results in Part A with the BID dosing regimen are of interest in terms of safety, PK, exposure, preliminary efficacy and any other relevant information such as data from patients treated with the QD regimen, and warrants further investigation, approximately 56 patients could be treated at the RD of amcenestrant after analysis of the Part A- BID to collect safety, PK and efficacy data. In Part D, approximately 28 patients will be treated at the selected RD(s). In Part G, approximately 34 patients are planned to be treated. In Part I, approximately 12 patients are planned to be treated. In Part K, approximately 20 patients are planned to be treated.

In cases where the risk of additional or unexpected toxicities is judged as being too high by the Study Committee, the continuation of the study at a dose below the predefined MTD, with or without corrective measures, could be decided by the Study Committee.

The occurrence of cumulative toxicity, and toxicities meeting the DLT criteria observed after Cycle 1, if any, will also be assessed.

6.7 GUIDELINES FOR MANAGEMENT OF ADVERSE EVENTS

This is a first-in-human study, therefore, so far, only limited clinical data are available for amcenestrant (eg, phototoxicity, gastrointestinal toxicities, changes in liver function, changes in hematological values). Based on preclinical data and clinical data from SERD, it is anticipated that amcenestrant related AEs could be managed by standard medical treatment/practice, which will also include but not limited to the provision of corrective treatment or medications, supportive care and dose omission. Each treatment intervention should be clearly documented. Investigators are encouraged to exercise their medical judgment in the management of the toxicities (see Section 6.5).

Because toxicity studies indicate a potential risk for phototoxicity, the patient should avoid direct exposure to natural or artificial sunlight during study treatment. It is recommended to advise to wear protective clothing, sunscreen, and lip balm with a high sun protection factor (eg, ≥30) to cover UVA and UVB when outdoors during treatment and until 5 days after treatment is completed.

6.8 DURATION OF STUDY PARTICIPATION

6.8.1 Duration of study participation for each patient

The patient will be considered in the study from informed consent signature until 30 days after last study treatment administration.

For Arm #3 parts **F and G only**: Testing for *PIK3CA* status for patients who have never undergone *PIK3CA* testing will be done locally prior to the main consenting process and beginning of the screening procedures. Only patients with a documented *PIK3CA* mutation, whether previously detected/confirmed by an old test or established by the *PIK3CA* testing in the pre-screening period, will be allowed to consent for study participation.

The duration of the study for an individual patient will include a period to assess eligibility (screening or baseline period) of up to 4 weeks (28 days), a treatment period of at least 1 cycle (28 days) of study treatment, and an EOT visit within 22 to 30 days following the last administration of study treatment (or until the patient receives another anticancer therapy, whichever is earlier). If further therapy is initiated before D22 after last IMP, investigator should contact the patient (either by phone call or visit) to obtain final collection of safety information (stabilization or recovery of TEAEs) within 30 days after last IMP intake or in follow up visit in case of ongoing SAE or related AE. Study treatment may continue until precluded by unacceptable toxicity, disease progression, or upon patient's request.

In Arms #2, #3, #4, and #5 (Parts C/D, F/G, H/I and J/K), if palbociclib/alpelisib/everolimus/ abemaciclib are prematurely permanently discontinued, amcenestrant can be continued until an EOT criterion is met. The end of study treatment visit in this case will be 30 days after the date of last amcenestrant administration.

Patients who discontinue the study treatment prior to documentation of PD will be followed every 2 months until disease progression or initiation of further anticancer therapy, or cut-off date (COD), whichever comes first.

The expected enrollment period is approximately 60 months.

There will be several cut-off-dates (COD) for this study:

1. In each study Arm dose escalation (Parts A, C, F, H and J), the first COD will be done at the end of the first cycle of the last patient treated in the given cohort study part in order to have at least the first cycle evaluable for all patients for determination of the MTD and for the RD.
2. The COD primary analysis, for each study Arm (ie, combined dose escalation and dose expansion), will be at each study Arm's LPI+12 months, except for Arm#2 which COD will be at LPI+20 months.
3. The final study COD will be performed when the last study Arm will have reached its COD.
4. In addition, for all study parts, informal analyses could be performed on as needed basis during the study to support further development of the compound and regulatory requirements.

After each study Arm COD, ongoing patients will receive study therapy until disease progression, occurrence of unacceptable toxicities, whichever is earlier, and they will only be followed for study treatment administration, SAEs, study treatment-related AEs and AEs leading to study treatment discontinuation.

6.8.2 Determination of end of clinical trial (all patients)

The end of study will occur when all patients have had the opportunity to complete the EOT visit 30 days after the last study treatment administration.

6.9 INTERIM ANALYSIS

Interim analyses of ORR (by RECIST v1.1) will be performed in Arm #1 Part B when 45 patients in the QD regimen. The procedure and criteria for undertaking an interim analysis are described in Section 13.10.

6.10 STUDY COMMITTEES

A Study Committee will be set up, which will include the investigators (or designee) who participate in dose escalation study parts, Sponsor representatives, and, if needed, the ad-hoc experts (eg, FES PET expert). The Study Committee will meet regularly during the dose escalation/safety run-in study parts. The Study Committee will review available clinical data including PK and safety data (especially DLTs) as well as FES-PET scan results for Arm#1 Part A of each individual patient who are treated in dose escalation study parts in order to adjust the number of enrolled patients at each dose level, as well as to decide the further dose escalation, if appropriate. Decisions regarding final dose selection will be made at the Dose Selection meeting which will be documented and shared with sites.

7 SELECTION OF PATIENTS

7.1 NUMBER OF PATIENTS

Refer to Section 13.1.

7.2 INCLUSION CRITERIA

I 01. Patients must be postmenopausal women as defined by one of the following:

a) Women >60 years

b) Women ≤60 years:

- With spontaneous cessation of menses >12 months prior to registration in the absence of chemotherapy, tamoxifen and toremifene.
- Or with cessation of menses of duration ≤12 months or secondary to hysterectomy AND have follicle stimulating hormone (FSH) level in the postmenopausal range according to institutional standards (or >34.4 IU/L if institutional range is not available) prior to registration.
- Or who have received hormonal replacement therapy but have discontinued this treatment AND have FSH level in the postmenopausal range according to institutional standards (or >34.4 IU/L if institutional range is not available) prior to registration.
- Or with status post bilateral surgical oophorectomy.
- Or are premenopausal women on a gonadotropin-releasing hormone (GnRH) analog for at least 6 months (to be continued during study treatment) and have a negative pregnancy test prior to initiation of study treatment and at monthly intervals during treatment. In Arm #3 (Parts F and G) only, patients and their male partners must agree to use non-oral contraception if sexually active during the treatment and 1 week after the last dose. In Arm #4 (Parts H and I) only, patients and their male partners must agree to use non-oral contraception if sexually active during the treatment and 8 weeks after the last dose. In Arm #5 (Parts J and K) only, patients and their male partners must agree to use non-oral contraception if sexually active during the treatment and 3 weeks after the last dose.

I 02. Patients with histological or cytological proven diagnosis of the breast adenocarcinoma with evidence of either locally advanced not amenable to radiation therapy or surgery in a curative intent, inoperable and/or metastatic disease.

I 03. Either the primary tumor or any metastatic site must be positive for ER (>1% tumor cell staining by IHC).

I 04. Either the primary tumor or any metastatic site must be HER2 non over expressing by IHC (0, 1+), or in situ hybridization-negative based on single-probe average HER2 copy number <4.0 signals/cell or dual-probe HER2/centromeric probe for chromosome 17 (CEP17) ratio <2 with an average HER2 copy number <4.0 signals/cell as per American Society of Clinical Oncology guidelines (39).

I 05. Prior chemotherapy for advanced disease is allowed. **Prior chemotherapy for advanced disease is not allowed in dose expansion of Arms #3, #4, and #5 (Part G, I and K respectively).** (NOTE: Antibody drug conjugates (ADCs) are considered as chemotherapy in this study):

- Patients must have received no more than 3 prior chemotherapeutic regimens in Arm #1 Part A (dose escalation, monotherapy).
- Patients must have received no more than 1 prior chemotherapeutic regimen in Arms #1, #2, #3, #4, and #5 (Parts B, C, D, F, H and J respectively).

I 06. Patients must have received at least 6 months of prior endocrine therapy for advanced breast cancer.

Dose Escalation study parts:

Arm #3: - **Part F**: up to 2 prior lines of either single endocrine therapy and/or endocrine-based therapy

Arm #4: - **Part H**: up to 2 prior lines of either single endocrine therapy and/or endocrine-based therapy (exemestane not allowed)

Arm #5: - **Part J**: up to 2 prior lines of either single endocrine therapy and/or endocrine-based therapy

Dose Expansion study parts:

Arm #2: - **Part D**: no more than 2 prior lines of advanced endocrine therapy for advanced disease are allowed

Arm #3: - **Part G**: patients must have received and progressed on the combination of Aromatase Inhibitors (AI) + CDK4/6 inhibitor as the first line (1L) treatment for advanced disease

Arm#4: - **Part I**: patients must have received and progressed on the combination of Aromatase Inhibitors (AI) + CDK4/6 inhibitor as the first line (1L) treatment for advanced disease (exemestane not allowed)

Arm#5: - **Part K**: up to 1 prior line of a single endocrine therapy for advanced disease

Note: Additional patients who relapsed while on previous adjuvant endocrine therapy that was initiated ≥24 months ago, OR relapsed <12 months after completion of adjuvant endocrine therapy are also allowed for Arms #2, #3, #4, and #5 (Parts C, D, F, G, H, I, J and K)

I 07. Age ≥18 years old.

I 08. Measurable lesion by RECIST v1.1 (Appendix C).

I 09. The patient is capable of understanding the informed consent and complying with the protocol and has signed the informed consent form (ICF) before any study (specific screening procedures or evaluations).

Arm #1 Part A only

I 10. Patient entering Part A must agree to undergo:

a) Two ^{18}F-FES-PET/CT imaging scans, one at baseline and one between Day 11 and Day 15 of study treatment intake and

b) Two FDG PET/CT for Part A BID, one at baseline and one between Day 11 and Day 15 of study treatment intake before ^{18}F-FES-PET (patients whose baseline FDG PET/CT results are negative for tumors will not be eligible), and

c) Paired biopsies (before treatment and during treatment): For baseline samples, formalin-fixed and paraffin-embedded (FFPE) archived biopsy samples (within past 3 months prior initiation of study treatment) can be used, but preferably fresh biopsies from primary tumor or recurrence or metastasis, will be collected. It is recommended that the end of Cycle 2 biopsy (on-treatment biopsy) be collected at the same location as the baseline biopsy, whenever the tumor is accessible and during treatment.

Arm #1 Part B

I 11. For patients who consent to paired biopsies (before treatment and during treatment): for baseline samples, formalin-fixed and paraffin-embedded (FFPE) archived biopsy sample can be used (within past 3 months prior initiation of study treatment) but preferably fresh biopsies from primary tumor or recurrence or metastasis will be collected. It is recommended that the end of Cycle 2 biopsy (on-treatment biopsy) be collected at the same location as the baseline biopsy, whenever the tumor is accessible during treatment.

Arm #3 Part F and G only

I 12. In **Parts F and G**, patient must have confirmed/detected *PIK3CA* mutation determined in tumor tissue and/or plasma cfDNA. The *PIK3CA* testing should be performed locally.

7.3 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.2 will be screened for the following exclusion criteria:

7.3.1 Exclusion criteria related to study methodology

E 01. Eastern Cooperative Oncology Group (ECOG) performance status ≥2 (see Appendix A).

E 02. Significant concomitant illness, including psychiatric condition that, in the opinion of the Investigator or Sponsor, would adversely affect the patient's participation in the study.

E 03. Medical history or ongoing gastrointestinal disorders potentially affecting the absorption of oral IMPs. Patients unable to swallow normally and to take capsules. Predictable poor compliance to oral treatment.

E 04. Any malignancy related to human immunodeficiency virus (HIV); or unresolved viral hepatitis.

E 05. Patients with a life expectancy less than 3 months.

E 06. Patients not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or patients potentially at risk of noncompliance to the study procedures (ie, unwillingness and inability to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions).

E 07. Major surgery within 4 weeks prior to first study treatment administration.

E 08. Patient with any other cancer. Adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer or any other cancer from which the patient has been disease free for >3 years are allowed.

E 09. Patient is the Investigator or any sub investigator, research assistant, pharmacist, study coordinator, or other staff or relative thereof directly involved in the conduct of the protocol.

Arm #1 Part A only

E 10. Patient with liver metastases only.

7.3.2 Exclusion criteria related to the disease

E 11. Patients with known brain metastases, leptomeningeal carcinomatosis or/and spinal cord compression. Patients with brain metastases that have been previously totally resected or irradiated are eligible provided no progression or relapse is observed within 4 weeks of the treatment.

E 12. Treatment with anticancer agents (including investigational drugs) less than 2 weeks before first study treatment administration (less than 4 weeks if the anticancer agents were antibodies).

E 13. Prior treatment with another selective ER down-regulator (SERD):

- Dose Escalation study parts **(Parts F, H and J)**: SERDs are not allowed except for fulvestrant which will need a washout of at least 6 weeks prior to the first study drug administration.
- Dose Expansion study parts **(Parts G, I and K)**: prior (last) treatment with any SERD including fulvestrant will not be allowed.

E 14. Inadequate hematological function including neutrophils $<1.5 \times 10^9$/L; platelet count $<100 \times 10^9$/L.

E 15. Prothrombin time: International normalized ratio >1.5 times the upper limit of normal (ULN) or out of therapeutic range if receiving anticoagulation that would affect the PT/INR.

E 16. Inadequate renal function with serum creatinine ≥1.5 x ULN or, if between 1.0 and 1.5 x ULN with eGFR <60 mL/min/1.73m^2 as estimated using the abbreviated Modification of Diet in Renal Disease formula (Appendix I).

E 17. Liver function: aspartate aminotransferase (AST) >3 x ULN, or alanine aminotransferase (ALT) >3 x ULN. Alkaline phosphatase (ALP) up to Grade 2 (2.5 to 5 x ULN), gamma glutamyl transferase (GGT) up to Grade 2 (2.5 to 5 x ULN) would be acceptable only if related to the presence of bone and/or liver metastases as judged by the Investigator. Total bilirubin >1.5 x ULN.

E 18. Patients with Gilbert disease.

E 19. Non-resolution of any prior treatment related toxicity to < Grade 2, except for alopecia according to the NCI-CTCAE v4.03 (Appendix B).

E 20. E20 criterion removed per amendment 10

E 21. a. All study parts, treatment with strong CYP3A inducers within 2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest (see Appendix E).

b. In Arm#1 (Part A and B) and Arm#5 (Part J and K, full PK sampling only), in patients with 4β-OH cholesterol assessment: Treatment with strong and moderate CYP3A inhibitors within 2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest (see Appendix E).

E 22. More than 1 prior advanced CDK4/6 inhibitor-based therapy in Arm #1, Arm #2 (Part C), Arm #3 (Parts F and G), and Arm#4 (Part H).

E 23. Treatment with strong CYP3A inhibitors within 2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest in Arm#2 (Parts C and D) only according to palbociclib labeling (Appendix E).

E 24. Medical conditions requiring concomitant administration of medications with a narrow therapeutic window metabolized by CYP3A and for which a dose reduction cannot be considered in Arm #2 (Part C and D) according to palbociclib labeling (see Appendix F).

E 25. Arm #2 (Part D) and Arm #5 (Parts J, and K) only: Prior therapy with targeted therapy for advanced disease (ie, CDK 4/6 inhibitors, PI3K inhibitors, mTOR inhibitors and AKT inhibitor)

Part E only (Canceled as per Amendment 08)

E 26. E26 criterion removed per Amendment 08.

E 27. E27 criterion removed per Amendment 08.

E 28. E28 criterion removed per Amendment 08.

E 29. E29 criterion removed per Amendment 08.

E 30. Arm #2, #3, #4 and #5 (**Part C, D, F, G, H, I, J, and K) only:** Patients with concurrent or history of pneumonitis

E 31. Arm #3, #4 and #5 (**Parts F, G, H, I, J and K) only**: prior treatment therapies that target the PI3K axis (mTOR inhibitors, AKT inhibitors, PI3K inhibitors)

E 32. Arm #3 and #4 (**Parts F, G, H, and I) only**: Patients with Diabetes Mellitus type-I or uncontrolled Diabetes Mellitus type-II: ie, fasting plasma glucose ≥140 mg/dL (7.7 mmol/L) or HbA1C >6.2%

E 33. Arm #3 and #4 (**Parts F, G, H, and I) only**: History of severe cutaneous reactions (eg, SJS, EM, TEN, DRESS)

E 34. Arm #3 (**Parts F and G) only**: Ongoing osteonecrosis of jaw

New Exclusion Criteria added in Amendment 09

E 35. **Arm #4 (Parts H and I)** only: Any active, untreated, or uncontrolled infection (eg, viral, bacterial, fungal etc.)

E 36. **Arm #4 (Parts H and I)** only: Patients with active and uncontrolled Stomatitis, Angioedema due to the concomitant treatment with ACE Inhibitors, impaired wounds

E 37. **Arm #4 (Parts H and I)** only: Uncontrolled Hypercholesterolemia, Hypertriglyceridemia and Hyperglycemia in non-diabetic patients

E 38. **Arm #4 (Parts H and I)** only: Treatment with strong or moderate CYP3A4 inhibitors, strong CYP3A4 inducers and/or P-gp inhibitors within 2 weeks before the first study treatment administration or 5 elimination half-lives, whichever is the longest

E 39. **Arm #5 (Parts J and K)** only: History or current (controlled/not controlled) Venous Thromboembolism (ie, Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), Cerebral Venous Sinus Thrombosis (CVST)

Patients who have been withdrawn from the study treatment cannot be reincluded in the study. Their inclusion and treatment numbers must not be reused.

New Exclusion Criterion added in Amendment 10

E 40. Treatment with drugs that are sensitive substrate of OATP1B1/1B3 (eg, asunaprevir, atorvastatin, bosentan, danoprevir, fexofenadine, glyburide, nateglinide, pitavastatin, pravastatin, repaglinide, rosuvastatin and simvastatin acid) within 5 days before first study treatment administration or 5 half-lives whichever is longer, and for which this drug cannot be replaced.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

If needed, the study drug may be supplied from the PI/site/Sponsor to the participants via a Sponsor-approved courier/delivery company as a Direct to Patient (DTP) delivery option if it is allowed by local regulations and agreed upon by the participant. Refer to Appendix J.

8.1.1 Pharmaceutical form

8.1.1.1 Amcenestrant

Amcenestrant will be supplied as 100 mg capsules.

8.1.1.2 Palbociclib

Palbociclib (Ibrance®) will be supplied as 75 mg, 100 mg and 125 mg capsules.

8.1.1.3 Alpelisib

Alpelisib will be supplied as 50 mg and 200 mg tablets.

8.1.1.4 Everolimus

Everolimus will be supplied as 5 mg tablets

8.1.1.5 Abemaciclib

Abemaciclib will be supplied as 50 mg, 100 mg, and 150 mg

8.1.2 Dose of drug per administration

During the first cycle visits (all parts) and first visit of the second cycle, study treatment should be administered at the clinics with dosing appropriately timed relative to blood sampling for the PK determination (Section 1.4). For all other days of treatment, patients can take their medication at home. For subsequent cycles, only Day 1 therapy may be given at the clinic. Therefore, in each case, patients will receive an adequate supply of capsules to take their medication at home for the remaining treatment duration.

8.1.2.1 Amcenestrant

The starting QD dose of amcenestrant is described in Section 6.2. Amcenestrant will be dispensed every 2 weeks.

In Arm #1 **Part A**, amcenestrant will be administered at assigned dose levels once daily, within a 28-day cycle. During Cycle 1, one dose will be taken on Day 1 in the fasted state, no dose on

Day 2 and the repeated once daily administration will start from Day 3. On Day 3 only, the dose will be taken in the fed state for a food effect evaluation, and then all subsequent administration will be taken in the fasted state, and at approximately the same time each day (±3 hours). If the patient vomits or misses a dose, an additional dose should not be taken and date and time of vomiting has to be recorded in the diary. The next prescribed dose should be taken at the usual time.

In the fasting condition, patients will receive the drug after an overnight fast of at least 10 hours with no food intake up to at least 3 hours following dosing on Days 1 and 22. On the other days, patients will receive the drug after an overnight fast of at least 10 hours with no food intake up to at least 2 hours following dosing (Table 18). The assigned daily dose is to be taken once in the morning, at approximately the same time each day (±3 hours), throughout treatment cycles. The appropriate daily dose of amcenestrant capsules is to be swallowed whole with a glass of noncarbonated water and a second glass of water is to be used to rinse out the mouth (for a total of approximately 240 mL). Patients should be instructed not to bite or chew on the capsules. In case of breakage of the capsules in the oral cavity, an additional glass of water should be taken immediately.

Table 18 - Fasting condition

	Fasted condition		
	Before drug adm	**After drug adm**	**Example**
Day 1 and Day 22 Cycle 1 (PK sampling)	Overnight fasting for approximately 10 hours	At least 3 hours	amcenestrant intake at 6:00 AM and breakfast at 9:00 AM Or amcenestrant intake at 8:30 AM with no breakfast before intake, lunch from 11:30 AM
Other days	Overnight fasting for approximately 10 hours	At least 2 hours	amcenestrant intake at 6:00 AM or 7:00 AM and breakfast at 8:00 AM or 9:00 AM, respectively

Fed conditions on Day 3 (Table 19) require a standard meal (total calorie of 400 to 500 kcal with approximately 27% fat content) ingested within 30 minutes after an overnight fast of at least 10 hours and amcenestrant administered within 5 minutes after meal completion. An example of the composition of this meal is described in Appendix D.

Table 19 - Fed condition

	Fed condition		
	Before drug adm	**After drug adm**	**Example**
Day 3, Cycle 1	5 minutes	N/A	Breakfast within 30 min from 8:00 AM to 8:30 AM with amcenestrant intake between 8:30 AM and 8:35 AM

In the fasting or fed condition, water will only be allowed ad libitum **after 2 hours postdosing**.

Pilot food effect: A pilot food effect will be assessed by PK sampling after drug administration with a standard meal on Day 3 of Cycle 1 in all patients treated in Part A. All other dosing in Part A will be taken in fasted condition. If results from the QD dosing regimen allow conclusions to be drawn, this will not be implemented for other dosing regimens (eg, BID) that are explored.

For **the BID** dosing regimen, amcenestrant will be administered once on Day 1, then BID from Day 3 onwards (no dose on Day 2) independent of food conditions at approximately the same time each day 12 hours apart (±1 hour).

Based on preliminary PK results observed in patients treated in Part A with the QD dosing regimen, less restrictive definitions were fixed for fasting and fed conditions for patients enrolled subsequently:

- Fasting condition: amcenestrant intake at least after 2 hours of fasting and at least 2 hours before next meal.
- Fed condition: amcenestrant intake less than 2 hours before or after meal.

In Arm #1 **Part B**, amcenestrant will be administered from Day 1 (without omission on Day 2) at the RD fixed in Part A, within a 28-day cycle, either in fasting or fed condition (as defined after preliminary PK results) even the days of PK sampling, and at approximately the same time each day (±3 hours). A BID regimen may also be explored if found to be needed.

In Arm #2, **Parts C and D**, amcenestrant will be administered from Day 1 at assigned dose levels, within a 28-day cycle in fed condition, and at approximately the same time each day (±3 hours). Amcenestrant and palbociclib must be taken together, 5 minutes apart. Both IMPs must be taken with food, regardless of the order of intake.

In Arm #3, **Parts F and G**, amcenestrant will be taken in fed condition QD from Cycle 1 Day 4 at 200 mg (or other amcenestrant doses) together with alpelisib 300 mg QD (or lower alpelisib doses) at approximately the same time each day (±3 hours) within a 28-day cycle. The days of PK assessment (ie, on C1D3 and C1D22) the drugs will have to be taken with a standard breakfast (see appendix D).

In Arm #4, **Parts H and I**, amcenestrant will be taken in fed condition QD from Cycle 1 Day 1 at 200 mg (or other amcenestrant doses) together with everolimus 10 mg QD (or lower doses) at approximately the same time each day (±3 hours) within a 28-day cycle. The days of PK assessment (ie, on C1D1 and C1D22) the drugs will have to be taken together with a standard breakfast.

In Arm #5, **Parts J and K**, amcenestrant will be taken in fed condition QD from Cycle 1 Day 1 at 200 mg (or other amcenestrant doses) together with abemaciclib 150 mg BID (or lower doses) at approximately the same time each day (±3 hours) within a 28-day cycle. In the morning, amcenestrant and abemaciclib will be administered together. The days of PK assessment (ie, on C1D1 and C1D22) the drugs will have to be taken together with a standard breakfast.

If a dose is vomited or omitted, the patient should not take the dose later or 2 doses at the next planned dose, and this information has to be recorded in the diary. Amcenestrant dose omission or reduction could occur in case of toxicity, as well as cycle delay in Arms #2, #3, #4, and #5 (see Section 6.5).

Advise to avoid sun exposure and wear protective clothing, sunscreen, and lip balm with high sun protection (eg, SPF ≥30) when outdoors during study treatment and 5 days after the last amcenestrant administration.

8.1.2.2 Palbociclib

The RD of palbociclib is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib should be taken with food at approximately the same time each day. Palbociclib will be dispensed every 4 weeks.

If the patient vomits or misses a dose, an additional dose should not be taken and this information has to be recorded in the diary. The next prescribed dose should be taken at the usual time. Palbociclib capsules should be swallowed whole (not chewed, crushed or opened prior to swallowing). Capsules should not be ingested if they are broken, cracked, or otherwise not intact.

The capsules should be swallowed with a full glass of water (not fruit juices).

8.1.2.3 Alpelisib

The RD of alpelisib is 300 mg. In both study parts, Part F (refer to the dose per pharmacy manual) and in Part G (refer to the dose per pharmacy manual) tablets should be taken orally once daily with food at approximately the same time each day.

Alpelisib will be dispensed every 4 weeks.

If the patient vomits or misses a dose, an additional dose should not be taken, and this information has to be recorded in the diary. The next prescribed dose should be taken at the usual time. Alpelisib tablets should be swallowed whole (not chewed or crushed).

The tablets should be swallowed with a full glass of water (not fruit juices).

8.1.2.4 Everolimus

Everolimus will be taken orally as 2x5 mg (10 mg) once a day at approximately the same time each day with food. Dose omission or reduction could occur in case of toxicity (see Section 6.5).

Everolimus will be dispensed every 4 weeks.

If the patient vomits or misses a dose, an additional dose should not be taken, and this information has to be recorded in the diary. The next prescribed dose should be taken at the usual time. Everolimus tablets should be swallowed whole (not chewed or crushed).

The tablets should be swallowed with a full glass of water (not fruit juices).

8.1.2.5 Abemaciclib

Abemaciclib will be taken orally, twice a day, with food as 2x100 mg and 2x150 mg, at approximately same times each day. Dose omission or reduction could occur in case of toxicity (see Section 6.5).

Abemaciclib will be dispensed every 4 weeks.

If the patient vomits or misses a dose, an additional dose should not be taken, and this information has to be recorded in the diary. The next prescribed dose should be taken at the usual time. Abemaciclib tablets should be swallowed whole (not chewed or crushed).

The tablets should be swallowed with a full glass of water (not fruit juices).

8.2 NON INVESTIGATIONAL MEDICINAL PRODUCT

Not applicable.

8.3 PACKAGING AND LABELING

Packaging is described in the pharmacy manual.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.4 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the study treatment in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of study treatment storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor in the Pharmacy Manual.

8.5 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the study treatment will be responsible for ensuring that the study treatment used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

The study treatment will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of study treatment issued and returned is maintained.

Any quality issue noticed with the receipt or use of a study treatment provided by the sponsor (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of study treatment may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall study treatment and eliminate potential hazards.

Under no circumstances will the Investigator supply study treatment to a third party, allows the study treatment to be used other than as directed by this clinical trial protocol, or dispose of study treatment in any other manner.

8.5.1 Treatment accountability and compliance

Administration of the study treatment will be supervised by the Investigator or sub-investigator.

The person responsible for drug dispensing is required to maintain adequate records of the study treatment. These records (eg, drug movement form) include the date the study treatment is received from the Sponsor, dispensed for patient, and destroyed or returned to the Sponsor. The packaging batch number (PR Nr) on the pack must be recorded on the drug accountability form.

Compliance to amcenestrant and palbociclib/alpelisib/everolimus/abemaciclib intake will be assessed using a patient diary and study medical record (study source documentation), which will document the return of any unused drug for compliance assessment. On Day 1, while the patient is in the clinic, the study staff will demonstrate to the patient how to record information on amcenestrant (for Arms #1 to #5), palbociclib (for Arm #2) and alpelisib (for Arm #3), everolimus (Arm #4) and abemaciclib (Arm #5) intake in the log. Patients will note every day the hours of study drug(s) intake or omission, if any. If vomiting occurs, they need to report the time and frequency in the same diary. In case of an early vomiting event, the administered dose of amcenestrant and/or palbociclib/alpelisib/everolimus/abemaciclib **should not be repeated**, and this information should be recorded in the diary. Patients will have to complete this log every day, for each dose and will return it to the study personnel at each visit, so that CRF can be completed on an ongoing basis.

Patients will be requested to return all unused amcenestrant and palbociclib/alpelisib/everolimus/abemaciclib to the study site at the end of the treatment period for each cycle for a full compliance assessment. Clinic staff will record the study medication dosing information including the actual clock time of each dose as per data recorded on the diary by the patient, or on the patient chart when the study medication is taken at site.

8.5.2 Return and/or destruction of treatments

Partially used and unused study treatment will be destroyed at the study site according to the standard practices of the site after an accurate accountability has been performed and signed by the Investigator (or the pharmacist). A detailed treatment log form of the destroyed study treatment will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

The Investigator must not destroy the unused study treatment unless Sanofi provides written authorization.

8.6 CONCOMITANT TREATMENT

A concomitant medication is any treatment received by the patient concomitantly to any study treatment(s).

All treatments being taken by the patient from the date of the consent form to the first study treatment administration, at any time during the treatment period and up to 30 days after the last dose are regarded as prior and concomitant treatments respectively and will be reported on the appropriate screen of the eCRF.

Premenopausal patients treated with a GnRH analog for at least 6 months to be eligible before study treatment initiation must continue this GnRH analog during study treatment period and should be reported as concomitant medications.

Special caution should be taken with regards to the following therapies for the amcenestrant treatment arm:

- Drugs that are sensitive substrates of CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 (See Appendix F) or UGTs since it may result in loss of efficacy of these agents.

In addition, for Part F and G (related to alpelisib administration):

- Avoid the use of BCRP inhibitors (See Appendix G). If unable to use alternative drugs, closely monitor for increased adverse reactions.
- Closely monitor when alpelisib is co-administered with CYP2C9 substrates (eg, warfarin or any other coumarin-derivative anticoagulant) (See Appendix G) which may decrease these drugs' plasma concentration and may reduce their activity. Alternatively, therapeutic anticoagulation may be accomplished by using low- molecular weight heparin or Direct Thrombin Inhibitors (DTIs) and Factor Xa inhibitors.
- Avoid the use of P-gp, BCRP and OAT3 substrates. In vitro evaluations indicated that alpelisib (and/or its metabolite BZG791) has a potential to inhibit the activities of OAT3 drug transporters and intestinal BCRP and P-gp. Alpelisib should be used with caution in combination with sensitive substrates of these transporters which exhibit a narrow therapeutic index because alpelisib may increase the systemic exposure of these substrates.
- Avoid the use of Herbal medications such as Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, black cohosh and ginseng due to their potential for complex interactions. Since cannabinoids have been shown to inhibit BCRP in vitro, medical cannabis should be used with caution. Patients should be closely monitored for increased adverse reactions (as the relevance of this interaction in vivo is currently unknown). In case of unexpected toxicities, patients should stop using all herbal medications. Use of all such medications (including frequency of administration) should be documented.
- Closely monitor when alpelisib is co-administered with bisphosphonates due to an increased risk of development of osteonecrosis of jaw (ONJ). For prevention and clinical management of ONJ, prescribing information of bisphosphonates should be followed.

- Avoid concomitant use of alpelisib with the following medicinal products: antipsychotics (haloperidol, ziprasidone, quetiapine, thioridazine, olanzapine, and risperidone), antiarrhythmics (amiodarone, sotalol, dofetilide, procainamide, quinidine, and flecainide), antibiotics (macrolides and fluoroquinolones), antidepressants (amitriptyline, imipramine, and citalopram), and other medicines such as, methadone, sumatriptan, ondansetron, cisapride. If the listed medicinal products still need to be used, caution and additional EKG monitoring should be used as clinically indicated.
- A maculopapular rash, pruritus, and dry skin, as the most frequent reported skin adverse events (only a minority present acneiform rash), can occur. The onset is typically within the first 2 months of treatment initiation and is reversible with adequate co-medication and alpelisib omission if needed. Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity at any grade and mandated if severe cutaneous reaction occurs. Workup for skin toxicity events may include a complete blood count with differential, and a full chemistry panel.
  Antihistamines administered prior to rash onset may decrease incidence and severity of rash; therefore, at the Investigator's discretion, non-sedating antihistamines (eg, cetirizine (Zyrtec©), loratadine (Claritin)) may be used as prophylactic treatment starting at Cycle 1 Day 1 to reduce severity of rash in all patients and especially for patients with a history of atopy such as allergic rhinitis, asthma, atopic dermatitis, or drug allergies. Recommended therapies for skin toxicity events of all grades and as clinically indicated include:
  - Consultation with a dermatologist should always be considered.
  - Mid to high potency topical steroids: triamcinolone 0.01% or fluocinonide 0.05% twice daily for at least 28 days. Recommend spray, lotion, or cream preparation for ease of application on trunk. For scalp involvement, recommend a foam or solution preparation.
  - Gamma-aminobutyric acid (GABA) Agonists: Gabapentin 300 mg every 8 hours, Pregabalin 50-75 mg every 8 hours (to adjust of renal impairment). Depending on patient's clinical condition, be aware of potential and common side effects observed with GABA agonists such as: somnolence, dizziness (both drugs) and peripheral edema (Gabapentin) among others adverse events.

  For Grade 4 skin events or any grade of severe cutaneous reactions (including SJS, TEN, EM, DRESS), alpelisib treatment must be permanently discontinued without any re-challenge.

  If dry skin is reported, it is recommended that patients with dry skin use mild and fragrance-free soaps and detergents.

In addition, in Arm #4 (Part H and I) (related to everolimus administration):

- The use of strong and moderate CYP3A4 inhibitors, including grapefruit and grapefruit juice (see Appendix E) and/or P-gp inhibitors is prohibited (see Appendix H)
- The use of strong CYP3A4 inducers is prohibited
- Avoid live vaccines and close contact with those who received live vaccines. Complete recommended childhood vaccinations prior to starting study treatment in order to prevent potential increased risk of infection or reduced immune response.

In addition, in Arm #5 (Part J and K) (related to abemaciclib administration):

- Avoid the use of strong CYP3A4 inhibitors
- Avoid the use of strong CYP3A4 inducers
- Avoid ingesting grapefruit and grapefruit juice

While participating in this study, patients may not receive any standard or investigational agents for treatment of their tumor other than the following treatments:

- Amcenestrant alone in Arm #1 (Parts A and B),
- Amcenestrant with palbociclib in Arm #2 (Parts C and D),
- Amcenestrant and alpelisib in Arm #3 (Parts F and G) of the study
- Amcenestrant with everolimus in Arm #4 (Parts H and I), and
- Amcenestrant with abemaciclib in Arm #5 (Parts J and K)

Any medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator, with the exception of those listed below.

Prohibited in all treatment arms:

- Systemic nonauthorized anticancer agents or concomitant radiotherapy (localized radiation therapy for pain control is permitted without any change in the study treatment).
- Among herbal medications and food products, it is recommended to avoid consumption of St John's Wort and genistein during treatment period.
- Patients should avoid direct exposure to natural or artificial sunlight during the study treatment period.
- The concomitant use of strong CYP3A4 inducers (see full list in Appendix E) since they may decrease amcenestrant exposure.
- Drugs that are sensitive substrates of OATP1B1/1B3 including asunaprevir, atorvastatin, bosentan, danoprevir, fexofenadine, glyburide, nateglinide, pitavastatin, pravastatin, repaglinide, rosuvastatin and simvastatin acid, since amcenestrant is a potential inhibitor and may decrease their elimination.

In addition, in Arm #1 Part A and B (for the 12 patients with full PK sampling) and Arm#5 Part J and K (for patients with full PK sampling):

- Initiation of any treatment with known strong and moderate CYP3A inhibitors (Appendix E) is not allowed 2 weeks before initiation and during Cycle 1. These treatments would interfere with 4β-hydroxy/ total cholesterol test interpretation.

In addition, for Arm #2 Parts C and D (from Cycle 2 if on combination with palbociclib) the following are also prohibited:

- Strong CYP3A4 inhibitors (see full list in Appendix E).
- Medications with narrow therapeutic window metabolized by CYP3A and for which a dose reduction cannot be considered (see full list in Appendix F).
- Grapefruit or grapefruit juice as it may increase plasma concentrations of palbociclib and should be avoided.

Patients taking any of the above medications at the time of the screening visit will be ineligible to enter study until administration of the prohibited agent can be safely discontinued, and an appropriate period of time has elapsed (2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest).

If a patient's clinical status requires administration of any of the above medications during the study, administration of the study drug should be stopped, and the patient will be withdrawn from the study. The change in clinical status mandating the use of the medication in question must be reported as the reason for study drug discontinuation.

8.7 POST INVESTIGATIONAL PRODUCT

As per discretion of the Investigator.

In case a new anticancer therapy is administered within 30 days of last study treatment administration or before recovery or consolidation of any related AEs or SAEs or before documented disease progression at the time of study treatment discontinuation, the date of start and the name of the new therapy will be collected in the eCRF.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 SAFETY

The major purpose of this Phase 1 study is to establish, based on DLTs, the MTD of amcenestrant, administered as monotherapy, then in combination with palbociclib, alpelisib, everolimus, and abemaciclib to postmenopausal women with advanced ER-positive breast cancer. Safety is thus the primary study endpoint and will be assessed continuously.

The safety profile will be assessed from the findings of physical examination (preferably by the same physician in each center), laboratory tests and reports of AEs, etc, and will be based on incidence, severity (as graded by the NCI-CTCAE v.4.03), and cumulative nature of treatment-emergent adverse events (TEAEs) (defined as AEs that develop or worsen in grade or become serious during the on-treatment period).

9.1.1 Dose-limiting toxicities

Arms #1, #2, #3, and #4 (Part A, C, F, H and J) only:

Potential Dose Limiting Toxicities (DLTs) are defined as the occurrence of any of the following treatment-emergent adverse events (TEAEs) related to the study therapy using NCI-CTCAE scale (version 4.03) during Cycle 1:

- Any Grade ≥3 nonhematological toxicity, **except:**
  - Grade 3 nausea and vomiting resolving to Grade ≤1 within 48 hours, with or without adequate antiemetic treatment (all study arms),
  - Grade 3 diarrhea, if controlled with adequate antidiarrheal therapy and lasting less than 48 hours (all study arms),
  - Grade 3 hyperglycemia resolving to Grade ≤1 within 48 hours, with or without adequate treatment (Arm #4 Part H only).
- Any Grade ≥3 hematological toxicity in all study arms, **except:**
  - Grade 3 anemia
  - Grade 4 neutropenia <7 days
  - Grade 3 neutropenia without fever or infection*
  - Grade 3 thrombocytopenia without bleeding
- Any elevated total serum bilirubin >2 x ULN in all study arms, except Part F
- Arm#3 (Parts F) only:
  - Grade 3 hyperglycemia (confirmed with a repeat FPG within 24 hours) not resolving to Grade ≤2 within 7 days after initiation of oral antidiabetic treatment, provided hyperglycemia did not lead to diabetic keto-acidosis, hospitalization for intravenous insulin infusion, or non-ketonic coma,
  - Grade 2 hyperglycemia (confirmed with a repeat FPG within 24 hours) not resolving to Grade ≤1 within 21 consecutive days (after initiation of oral antidiabetic treatment),

- Grade 2 ALT increase in conjunction with total blood bilirubin Grade ≥2 of any duration in the absence of liver metastases,
- Grade ≥3 ALT and/or AST increase for more than 4 consecutive days,
- Grade 3 Rash and Maculopapular Rash not resolving to Grade ≤1 within 7 days, with or without adequate treatment (including systemic steroid use as per protocol).

- Any toxicity related to study treatment, resulting in omission of the study treatment for 7 days or more during Cycle 1, or in Cycle 2 delay of more than 2 weeks in Arm #2 Parts C.
- A TEAE that in the opinion of the Study Committee is possibly or probably study treatment-related and of potential clinical significance such that further dose escalation would expose patients to unacceptable risk.

* G-CSF may be used to treat patients who have developed dose-limiting neutropenia, as per institutional guidelines (for Arm#3, alpelisib should be discontinued as per dose modification recommendations).

DLTs will be considered as adverse event of special interest (AESI). As such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of each event. The Investigator will attach the DLT-specific eCRF page to the transmitted DLT/AESI form or will complete the specific DLT form in the eCRF.

These TEAE(s) will be considered as study treatment-related in the absence of evidence to the contrary and if not related to disease progression. If multiple toxicities are seen, the presence of DLT will be based on the most severe experienced toxicity. At the end of Cycle 1, each patient must be assessed by the Investigator as to whether or not the patient experienced DLT, and this information must be recorded on the appropriate screen of the eCRFs, and an electronic DLT notification (either DLT or not) will be sent to the Sponsor.

The reported potential DLTs will be reviewed by the Study Committee in order to determine their relationship to the study treatment.

9.1.2 Adverse events

Adverse events will be collected from the signing of the study main informed consent up to 30 days after the last study treatment administration. During the follow-up period, ongoing SAEs regardless of relationship to study treatment and ongoing or new study treatment related AEs will be followed until resolution or stabilization. Adverse events encountered before the start of study treatment will be summarized separately.

Adverse events will be graded according to the NCI-CTCAE v.4.03 (Appendix B), and will be coded to a “Preferred Term” and associated primary “System Organ Class” using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be summarized with respect to the type, frequency, severity, seriousness, and relatedness.

The study-specific and general safety criteria are developed in Section 10.

9.1.3 Laboratory safety variables

Please refer to Study Procedures Section 12.

9.1.4 Clinical examinations

Please refer to Study Procedures Section 12.

9.1.5 Other safety endpoints

Please refer to Study Procedures Section 12.

9.2 PHARMACOKINETIC EVALUATION

9.2.1 Sampling time and sample blood volume

It is of utmost importance to collect all blood samples at the specified times and according to the specifications.

Samples missed or lost, for any reason should be recorded. Actual times of blood collection should be recorded in the eCRF. The days of sampling and times of drug administration should also be precisely recorded for the day of PK (Days 1, 3, 8, 11 to 15, 22) as well as the day before (Day 2 in Part A and Days 7, 21, 28) and after (Day 4 in Part A and Day 23).

In Part A, for the 6 patients treated in the BID dosing regimen, the PK/PD Flow chart of Part A (Section 1.4.1.1) will be used. Some PK samples will not be collected: Day 3 PK profile (from P12 to P22) and Day 22-T24h sample (P35).

The sampling times for blood collection can be found in the PK Flow Chart (Section 1.4).

The tables below summarize the sampled blood volume per patient during all treatment arms (Part A, B, C, D, F, G, H, I, J and K):

Table 20 - Blood sample volume collected per patient during study Arm #1 Part A

	Volume (mL)/sample	Number of samples	Volume (mL)/patient
PK amcenestrant	2 mL	37	74
	TOTAL volume		74 mL

Table 21 - Blood sample volume collected per patient during study Arm #1 Part A, BID regimen

	Volume (mL)/sample	Number of samples	Volume (mL)/patient
PK amcenestrant	2 mL	25	50
	TOTAL volume		50 mL

Table 22 - Blood sample volume collected per patient during study Arm #1 Part B

		Volume (mL)/sample	Number of samples[a]	Total volume (mL)/patient
PK amcenestrant	Full sampling	2 mL	23	46 mL
	Sparse sampling	2 mL	13	26 mL

4β-hydroxycholesterol will be assayed in the same tubes as the amcenestrant for the 12 patients with full PK sampling schedule only.
a At least 12 patients will undergo a full PK sampling schedule, remaining patients will follow a sparse sampling schedule

Table 23 - Blood sample volume collected per patient during study Arm #2 Part C

	Volume (mL)/sample	Number of samples	Volume (mL)/patient
PK amcenestrant and palbociclib	2 mL	23[a]	46
	TOTAL volume		46 mL

a in case of BID dosing regimen, the number of PK samples would be 21, thus a total of 42 mL per patient

Table 24 - Blood sample volume collected per patient during study Arm #2 Part D

		Volume (mL)/sample	Number of samples[a]	Total volume (mL)/patient
PK amcenestrant and palbociclib	Full sampling	2 mL	23[b]	46
	Sparse sampling	2 mL	13	26 mL

a At least 12 patients will undergo a full PK sampling schedule, remaining patients will follow a sparse sampling schedule.
b In case of BID dosing regimen, the number of PK samples would be 21, thus a total of 42 mL per patient.

Table 25 - Blood sample volume collected per patient during study Arm #3 (Part F and G)

		Volume (mL)/sample	Number of samples	Volume (mL)/patient
PK amcenestrant and alpelisib	Full sampling[a]	2 mL	21	42 mL
	Sparse sampling	2 mL	10	20 mL

a 18 patients will undergo a full PK sampling schedule, remaining patients will follow a sparse sampling schedule.

Table 26 - Blood sample volume collected per patient during study Arm #4 (Part H and I)

	Volume (mL)/sample	Number of samples	Volume (mL)/patient
PK amcenestrant and everolimus	2 mL	19	38 mL

Table 27 - Blood sample volume collected per patient during study Arm #5 (Part J and K)

		Volume (mL)/sample	Number of samples	Volume (mL)/patient
PK,amcenestrant, abemaciclib and its metabolites (M2, M18, M20)	Full sampling	3 mL	20	60 mL
	Sparse sampling	3 mL	10	30 mL

9.2.2 Pharmacokinetic sample handling procedure

Detailed instructions for PK sample preparation, storage, and shipping are summarized in Table 28, Table 29, Table 30, Table 31, Table 33, and Table 34. Further details will be provided to the study sites in a separate Laboratory Manual.

Table 28 - Summary of blood sample handling procedures for amcenestrant (Arm #1 Part A)

Blood sample volume:	2 mL
Anticoagulant tube type:	Blood will be collected into tubes with K2EDTA
Handling procedures:	Keep blood on ice until plasma harvest (must be within 30 minutes of blood sampling time) by centrifugation at approx. 1500 g for approx. 10 minutes at 4°C.
Plasma aliquot split:	2 aliquots, 500 µL in aliquot 1 and the remaining in aliquot 2.
Plasma storage conditions:	Polypropylene tubes with screw caps and frozen promptly (within 30 minutes of plasma preparation between -60°C and -80°C).
Plasma shipment conditions:	Frozen in dry ice

See lab manual for details concerning handling procedures.
K2EDTA = di-potassium ethylene diamine tetra-acetic acid

Table 29 - Summary of blood sample handling procedures for amcenestrant and metabolic profiling (Arm #1 Part B)

Blood sample volume:	2 mL
Anticoagulant tube type:	Blood will be collected into tubes with K2EDTA.
Handling procedures:	Keep blood on ice until plasma harvest (must be within 30 minutes of blood sampling time) by centrifugation at approx. 1500 g for approx. 10 minutes at 4°C.
Plasma aliquot split:	3 aliquots (only 2 aliquots for Part B sparse sampling schedule), 300 µL each in aliquots 1 and 2 (for amcenestrant) and the remaining in aliquot 3 (for metabolic profiling; only for full PK sampling schedule), Only 2 aliquots for Part B sparse sampling schedule with 500 µL in aliquot 1 and the remaining in aliquot 2.
Plasma storage conditions:	Polypropylene tubes with screw caps and frozen promptly (within 30 minutes of plasma preparation between -60°C and -80°C.
Plasma shipment conditions:	Frozen in dry ice.

See lab manual for details concerning handling procedures.
K2EDTA = di-potassium ethylene diamine tetra-acetic acid

Plasma will be kept for metabolic profiling (Arm #1 Part B only, ie, expansion phase of monotherapy). Data obtained from exploratory analysis will not be included in the clinical study report (CSR).

Table 30 - Summary of blood sample handling procedures for amcenestrant and palbociclib (Arm #2 [Parts C and D])

Blood sample volume:	2 mL
Anticoagulant Tube Type:	Blood will be collected into tubes with K2EDTA.
Handling procedures:	Keep blood on ice until plasma harvest (must be within 30 minutes of sampling time) by centrifugation at approx. 1500 g for approx. 10 minutes at 4°C.
Plasma aliquot split:	3 aliquots (only 2 aliquots for sparse sampling schedule), 300 µL each in aliquots 1 and 2 (for amcenestrant) and the remaining in aliquot 3 (for palbociclib; only in the full sampling schedule).
Plasma storage conditions:	Polypropylene tubes with screw caps and frozen promptly (within 30 minutes of plasma preparation between -60°C and -80°C, aliquot for palbociclib stored at -20°C.
Plasma shipment conditions:	Frozen in dry ice.

See lab manual for details concerning handling procedures. K2EDTA = di-potassium ethylene diamine tetra-acetic acid

Table 31 - Summary of blood sample handling procedures for amcenestrant (Arm #3, #4, and #5 [Parts F to Part K])

Blood sample volume:	1 mL
Anticoagulant Tube Type:	Blood will be collected into tubes with K2EDTA.
Handling procedures:	Keep blood at room temperature until plasma harvest (must be within 30 minutes of sampling time) by centrifugation at approx. 1500 g for approx. 10 minutes at room temperature.
Plasma aliquot split:	1 aliquot
Plasma storage conditions:	Polypropylene tubes with screw caps and frozen promptly (within 30 minutes of plasma preparation at -20°C or lower.
Plasma shipment conditions:	Frozen in dry ice.

See lab manual for details concerning handling procedures. K2EDTA = di-potassium ethylene diamine tetra-acetic acid

Table 32 - Summary of blood sample handling procedures for alpelisib (Arm #3 [Parts F and G])

Blood sample volume:	1 mL
Anticoagulant Tube Type:	Blood will be collected into tubes with K2EDTA.
Handling procedures:	Keep blood at room temperature until plasma harvest (must be within 30 minutes of sampling time) by centrifugation at approx. 1500 g for approx. 10 minutes at room temperature.
Plasma aliquot split:	2 aliquots
Plasma storage conditions:	Polypropylene tubes with screw caps and frozen promptly (within 30 minutes of plasma preparation) at -20°C or lower.
Plasma shipment conditions:	Frozen in dry ice.

See lab manual for details concerning handling procedures.
K2EDTA = di-potassium ethylene diamine tetra-acetic acid

Table 33 - Summary of blood sample handling procedures for everolimus (Arm #4 [Parts H and I])

Blood sample volume:	1 mL
Anticoagulant Tube Type:	Blood will be collected into tubes with K2EDTA.
Handling procedures:	Everolimus: after blood homogenization, five drops of 10 µL of liquid blood will be deposited into filter paper Whatman 903™ and let dried at room temperature for at least 2 hours. The remaining liquid blood samples are guard samples. They must remain stored in the BA lab until the end of the analysis of the DBS samples.
DBS sample:	1 card
DBS storage condition:	After drying the DBS card and a desiccant will be introduced into a Ziploc bag and stored at room temperature.
Liquid blood storage conditions:	Liquid blood samples will be frozen at -60°C or lower.
DBS shipment conditions:	Room temperature.
Liquid blood shipment conditions:	Frozen in dry ice.

See lab manual for details concerning handling procedures.

Table 34 - Summary of blood sample handling procedures for abemaciclib and its metabolites M2, M18, M20 (Arm #5 [Parts J and K])

Blood sample volume:	2 mL
Anticoagulant Tube Type:	Blood will be collected into tubes with K2EDTA.
Handling procedures:	Keep blood on ice until plasma harvest (must be within 30 minutes of sampling time) by centrifugation at approx. 1500 g for approx. 10 minutes at 4°C.
Plasma aliquot split:	2 aliquots, 500 µL each in aliquots.
Plasma storage conditions:	Polypropylene tubes with screw caps and frozen promptly (within 30 minutes of plasma preparation between -20°C or lower).
Plasma shipment conditions:	Frozen in dry ice.

See lab manual for details concerning handling procedures.

Table 35 - Summary of blood sample handling procedures for 4β-OH cholesterol and total cholesterol (Arm #5 [Parts J to Part K])

Blood sample volume:	1 mL
Anticoagulant Tube Type:	Blood will be collected into tubes with K2EDTA.
Handling procedures:	Keep blood at room temperature until plasma harvest (must be within 30 minutes of sampling time) by centrifugation at approx. 1500 g for approx. 10 minutes at room temperature.
Plasma aliquot split:	1 aliquot
Plasma storage conditions:	Polypropylene tubes with screw caps and frozen promptly (within 30 minutes of plasma preparation at -20°C or lower.
Plasma shipment conditions:	Frozen in dry ice.

See lab manual for details concerning handling procedures.
K2EDTA = di-potassium ethylene diamine tetra-acetic acid

Incurred sample reproducibility analysis for amcenestrant, palbociclib, alpelisib, everolimus and abemaciclib will be performed on selected samples in order to assess the reliability of all sample concentration data. These analyses will be reported in addition to the final concentration data.

9.2.3 Bioanalytical method

Table 36 summarizes the bioanalytical methods to be used for quantifying amcenestrant, palbociclib, alpelisib and 4β-hydroxy/ total cholesterol in plasma. Table 37 summarizes the bioanalytical methods to be used for quantifying everolimus in whole blood and abemaciclib and its M2, M18 and M20 metabolites in plasma.

Table 36 - Bioanalytical method for amcenestrant, palbociclib, alpelisib, 4β-hydroxycholesterol and total cholesterol in plasma

Analyte	Amcenestrant	Palbociclib	4β-hydroxycholesterol and total cholesterol	Alpelisib
Matrix:	Plasma	Plasma	Plasma	Plasma
Analytical technique:	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Lower limit of quantification[a]:	5 ng/mL	1 ng/mL	4 ng/mL	5 ng/mL
Site of bioanalysis:	Pyxant, (SLC, US)	Pyxant, (SLC, US)	Pyxant, (SLC, US)	Pyxant (SLC, US)

a For amcenestrant, palbociclib and alpelisib, the LLOQs are given as target.

Table 37 - Bioanalytical method for everolimus, abemaciclib and its metabolites

Analyte	everolimus	Abemaciclib and its M2, M18 and M20 metabolites
Matrix:	Whole blood	Plasma
Analytical technique:	LC-MS/MS	LC-MS/MS
Lower limit of quantification[a]:	0.5 ng/mL	1 ng/mL
Site of bioanalysis:	LabCorp, (Indi, US)	Pyxant (SLC, US)

a For everolimus and abemaciclib, the LLOQs are given as target.

9.2.4 Urine sampling times and handling procedures

Urine samples will be collected from at least 12 patients selected for the full PK design after QD administration at the times specified in Table 38, for analysis of the parent compound during Part B, ie, the expansion phase of amcenestrant monotherapy.

Amcenestrant assay in urine will be performed using a fit-to-purpose method.

Table 38 - Urine sampling times

Day	Interval	Drug administration	Sample ID
Day 22 (first cycle only)	0-24 h	amcenestrant	U00

The handling procedures for urine samples are described in Table 39.

Table 39 - Urine handling procedure

Urine handling procedures	Keep at +4°C during collection interval. For each patient, at the end of the collection period, combine the urine fractions from that period and mix thoroughly. Record the total weight (or volume) of urine collected during each collection period in the CRF.
Urine sample volume	2 aliquots of 5 mL
Urine storage conditions	Keep in upright position between -60°C and -80°C

Detailed instructions for urine sample collection, sample storage and shipping will be provided to the study sites in a separate laboratory manual.

9.2.5 Pharmacokinetic parameters

Pharmacokinetic analyses will be carried out at the Sponsor by Pharmacokinetics, Dynamics and Metabolism (PKDM) department. Pharmacokinetic parameters will be determined by non-compartmental analysis using PKDMS (running Phoenix® software) for patients undergoing a full PK sampling scheme. Other patients may be analyzed using a population PK approach.

The parameters will include, but may not be limited to the following:

Table 40 - List of pharmacokinetic parameters and definitions

Parameters	Drug	Matrix	Definition/calculation
C_{max}	amcenestrant, palbociclib, alpelisib, everolimus, abemaciclib, M2, M18 and M20	Plasma, blood[a]	Maximum concentration observed
C_{trough}	amcenestrant	Plasma	Plasma concentration observed just before treatment administration during repeated dosing
AUC_{0-12}	amcenestrant, abemaciclib, M2, M18 and M20	Plasma	Area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (12 hours)
AUC_{0-24}	amcenestrant, palbociclib, alpelisib, everolimus	Plasma, blood[a]	Area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (24 hours)
AUC	amcenestrant, (Part A, Day 1 only)	Plasma	Area under the plasma concentration versus time curve extrapolated to infinity according to the following equation: $AUC = AUC_{last} + \frac{C_{last}}{\lambda_Z}$ Values with percentage of extrapolation >30% will not be reported
AUC_{last}	amcenestrant		Area Under the Concentration versus time curve calculated using the trapezoidal method from time 0 to the real time tlast

Parameters	Drug	Matrix	Definition/calculation
CL/F (Part A, Day 1 only)	Amcenestrant	Plasma	Apparent total body clearance of a drug from the plasma calculated using the following equation: $CL/F = \frac{Dose_{EV}}{AUC}$
CL_{ss}/F	Amcenestrant, palbociclib, alpelisib, everolimus	Plasma, blood[a]	Apparent total body clearance after repeated extra-vascular (EV) doses of a drug at steady state from the matrix (plasma) calculated using the following equation: $CL_{ss}/F = \frac{Dose_{EV}}{AUC_{0\text{-}\tau EV}}$
t_{lag}	Amcenestrant	Plasma	Lag time, interval between administration time and the sampling time preceding the first concentration above the lower limit of quantification
t_{max}	Amcenestrant, palbociclib, alpelisib, everolimus, abemaciclib, M2, M18 and M20	Plasma, blood[a]	First time to reach C_{max}
$t_{1/2z}$	Amcenestrant (Part A, Day 1 only)	Plasma	Terminal half-life associated with the terminal slope (λz) determined according to the following equation: $t_{1/2Z} = \frac{0.693}{\lambda_z}$ where λz is the slope of the regression line of the terminal phase of the plasma concentration versus time curve, in semi logarithmic scale. Half-life is calculated by taking the regression of at least 3 points.
$Ae_{0\text{-}24}$ (Arm #1 Part B, Day 22 only)	Amcenestrant	Urine	Cumulated amount excreted in urine from time 0 to 24 hours after the drug administration on Day 1
$fe_{0\text{-}24}$ (Arm #1 Part B, Day 22 only)	Amcenestrant	Urine	Fraction of dose excreted in urine from time 0 to 24 hours after the drug administration on Day 1
$CL_{R\ 0\text{-}24}$ (Arm #1 Part B, Day 22 only)	Amcenestrant	Urine	Renal clearance of the drug determined in the 0-24 hour interval, according to the following equation: $CL_{R0\text{-}t} = \frac{Ae_{0\text{-}t}}{AUC_{0\text{-}t}}$

a blood matrix is for everolimus assay only

9.3 PHARMACOGENETIC ASSESSMENT

9.3.1 Optional drug metabolizing enzymes and transporters DNA sample

For those patients who select to do the optional pharmacogenetic assessment in the Main ICF, at the study visit as specified in the study flow chart, a blood sample will be collected to investigate pharmacogenetic variants related to ADME (Absorption, Distribution, Metabolism, Excretion) using validated methods as intrinsic factors potentially associated with pharmacokinetic and pharmacodynamic variability of amcenestrant.

Special procedures for collection, storage and shipping of DNA pharmacogenetic samples will be described in a separate laboratory manual which will be available at the investigational site.

9.4 PHARMACODYNAMIC ASSESSMENTS

See Section 1.4 for the scheduling of PD assessments.

9.4.1 18 fluorestradiol-positron emission tomography and 18 fluorodesoxyglucose scans (Part A only)

Inhibition of ER occupancy investigation using ^{18}F-FES-PET imaging is a limited invasive procedure that allows assessment of ER presence by assessing the binding of radiolabelled estradiol, the ligand of ER (signal extinction). ER-positive tumor sites will be detected with ^{18}F-FES-PET/CT scan imaging at baseline and will be compared to a scan evaluated at steady state. For patients on a QD regimen, the second scan will be performed after at least 8 continuous days of treatment (ie, between Day 11 and Day 15) and between 16 to 24 hours after the previous administration of the study drug, with a time window of 2 hours around 24 hour theoretical time. For patients on a BID regimen, the second scan will be performed after at least 8 continuous days of treatment (ie, between Day 11 and Day 15) and between 7 to 12 hours after the previous administration of the study drug. In case of limited response observed by PK and ^{18}F-FES-PET, a twice daily schedule of administration will be considered for the RD decision after using ^{18}F-FES-PET at an earlier time window. Patients should be instructed to take the previous study treatment dose at the appropriate time in line with availability of the PET/CT scan at sites. The signal extinction between baseline and on study treatment ^{18}F-FES-PET scans (ΔSUV) will constitute the PD readout of the ER engagement. A decrease ≥90% inhibition of SUV should represent an inhibition of the estrogen ligand binding or the near-to complete degradation of ER. The ^{18}F-FES-PET will follow the extent of ER inhibition and this will help with the RD decision. No ^{18}F-FES-PET imaging will be performed in Arm #1 and #2 (Parts B, C, or D).

All the procedures concerning the ^{18}F-FES-PET and FDG scans will be described in a specific manual.

9.4.2 Estrogen receptor 1 gene mutation status in circulating free DNA

ESR1 mutations have emerged as a resistance mechanism to endocrine therapies. While rare or absent in naïve patients, an average of 25% to 35% of patients with ER+ breast cancer tumors will acquire a dominant activating mutation of ESR1, the gene encoding ER, after prolonged/repeated treatment with endocrine therapies (in particular AI). The presence of ESR1 mutation is linked to a poor prognosis.

ESR1 activating mutations emerge essentially in the ligand domain and render the ER ligand independent, therefore less sensitive to ligand competing endocrine therapies.

Twelve independent mutations of ESR1 gene, including the hotspot mutations described in the ligand domain, will be determined in all patients at baseline and at end of Cycle 2 by multiplex droplet digital polymerase chain reaction (ddPCR) from plasma extracted cfDNA. For Parts F, G, H, I, J and K, ESR1 mutation will be provided by cfDNA NGS mutation profile also used for *PI3KCA* assessment.

The impact of ESR1 mutation status on clinical outcomes in patients treated by the monotherapy amcenestrant or by amcenestrant in combination with palbociclib at RD will also be assessed in the ESR1 wild type and the ESR1 mutated population separately.

Special procedures for collection, handling, storage and shipment will be described in a separate laboratory manual which will be available at the investigational site.

9.4.3 Mutational profiling in circulating free DNA

Cancer gene mutation present in the tumor at baseline might influence the response to amcenestrant. It is also possible that emergent mutation might constitute the root cause of the escape mechanism to amcenestrant treatment. To evaluate and generate hypothesis on both intrinsic and emerging resistance mutations, the plasma of all patients treated in this study will be collected at baseline and at the EOT and cfDNA will be extracted. For Parts F, G, H, I, J and K plasma will be collected in all patients to monitor the molecular profile of the tumor in cfDNA at Screening, end of Cycle 2 and 4 (at the time of tumor assessment) and at the EOT/progression. Saliva will be collected at baseline in order to extract germline DNA which will be used as a reference to subtract single nucleotide polymorphisms in the mutational analysis. The mutation status of a limited number of cancer genes will be determined by next generation sequencing (NGS) and will be used to explore the potential link between specific mutation and intrinsic or acquired resistance to the amcenestrant treatment. The list of genes will include but is not limited to ESR1, PI3K and the p53 pathways.

Special procedures for collection, handling, storage and shipment will be described in a separate laboratory manual which will be available at the investigational site.

9.4.4 Tumor biopsy to assess estrogen receptor degradation (Arm #1, #3, #4, and #5 [Part A BID, Parts B, F G, H, I, J, and K])

While the ^{18}F-FES-PET imaging can assess ER accessibility to its ligand estrogen, it does not constitute the formal proof that our agent is readily degrading ER in tumors. In all patients in Arm #1 (Part A and in at least 10 patients in Part B [optional]), and Arm #3, #4, and #5 (F, G, H, I, J, and K [optional]) with accessible tumor will be asked to contribute the most recent archived biopsied tumor (within past 3 months prior to initiation of study treatment) or preferably to a fresh tumor biopsy at baseline. In addition, during treatment, these patients will be asked to provide a biopsy of either a primary or secondary tumor site at the end of Cycle 2. The collected tissue should be fixed and preserved. Approximately 9 FFPE slides (5 micron each for IHC analysis) and 3 FFPE slides (10-micron each for RNA analysis, if possible) will be collected for each biopsy. The presence of ER will be determined by central IHC and the ER results at baseline and on treatment will be compared to assess ER degradation. In addition, expression levels of Ki67, Bcl-2, PgR and potentially other proteins (eg, Cyclin D1) that may be related to cancer will also be evaluated by IHC, and tumor gene expression profiles will be obtained.

9.4.5 Estradiol

Estradiol is the natural ligand to ER and amcenestrant antagonizes the binding of estradiol to ER. Estradiol will be assayed to explore possible influence of circulating levels of estradiol on preliminary efficacy. Circulating estradiol will be measured before and after treatment.

Special procedures for collection, handling, storage and shipment will be described in a separate laboratory manual which will be available at the investigational site.

9.5 SAMPLED BLOOD VOLUME

Table 41 summarizes the volume of blood to be collected during Cycle 1 and further cycles, as appropriate in all treatment arms.

Table 41 - Sampled blood volume during the study

Type	Volume per sample	Part A		Part B		Part C		Part D		Part F and G		Part H and I		Part J and K	
		Number of samples	Volume per patient	Number of samples	Volume per patient	Number of samples	Volume per patient	Number of samples	Volume per patient	Number of samples	Volume per patient	Number of samples	Volume per patient	Number of samples	Volume per patient
Optional for DMET/ADME genotyping	6 mL	1	6 mL	1	6 mL	1	6 mL	1	6 mL	1	6 mL	1	6 mL	1	6 mL
PK sample amcenestrant and/or palbociclib	2 mL	37[a]	74 mL	23[b]	46 mL	23	46 mL	23[b]	46 mL						
PK sample amcenestrant and/or alpelisib	2 mL									21	42 mL				
PK sample amcenestrant and everolimus	2 mL											19	38 mL		
PK sample amcenestrant and abemaciclib	3 mL													20	60 mL
PK sample 4βOH-cholesterol and total cholesterol	1 mL													3	3ml
PD sample (cfDNA for ESR1 status)	10 mL	2	20 mL	2	20 mL	2	20 mL	2	20 mL						
PD sample (cfDNA for mutational profiling)	10 mL	2	20 mL	2	20 mL	2	20 mL	2	20 mL	4	40 mL	4	40 mL	4	40 mL
PD sample (Estradiol)	2 or 4 mL	-	-	2	4 mL	-	-	2	4 mL	2	8 mL	2[c]	8 mL	2[c]	8 mL
Total		42	120 mL	30	96 mL	28	92 mL	30	96 mL	28	96 mL[d]	26	92 mL[e]	30	117 mL[f]

CfDNA = circulating free DNA; DMET = drug metabolizing enzymes and transporters; PD = pharmacodynamics; PK = pharmacokinetic

a If amcenestrant is taken in a BID regimen, the number of PK samples would be 25 in Part A, thus a total of 50 mL per patient for a total of 96 mL.

b For Arm #1 and #2 (Part B and D), at least 12 patients will undergo a full PK sampling schedule with 23 samples collected. Remaining patients will follow a sparse sampling schedule with 13 samples collected, thus for a total volume of 26 mL per patient for PK samples.

c For dose expansion only (Part I and K)

d For Arm #3 Part G, up to 12 patients will undergo a full PK sampling schedule. Remaining patients will follow a sparse sampling schedule with 10 sample collected for amcenestrant assay, thus total blood volume per patient will be 54mL.

e For arm#4, Part H the total blood volume per patient will be 64 mL as PD sample for estradiol is collected in Part I only

f For arm#5, Part J the total blood volume per patient will be 89 mL as PD sample for estradiol is collected in Part K only. In Part K, patients under sparse sampling schedule 10 sample will be collected for amcenestrant assay and no PK sample for 4βOH-cholesterol and total cholesterol; the total blood volume per patient will be 64 mL

9.6 FUTURE USE OF SAMPLES

Not all the samples collected during this study may be required for the tests planned in this clinical trial. For subjects who have consented to it, the samples that are unused or are leftovers from the used samples, may be used for oncology-related research (excluding genetic analysis providing information on the likelihood of developing diseases), and other research purposes than those defined in the present protocol.

These other research analyses will help to understand either disease subtypes or drug response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers.

These samples will remain labelled with the same identifiers used during the study (ie, Subject ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting subject confidentiality and personal data (see Section 16.3 and Section 16.5).

9.7 EFFICACY (ALL STUDY PARTS)

9.7.1 Criteria for response (antitumoral activity)

RECIST v1.1 (Response Evaluation Criteria In Solid Tumors) will be followed for assessment of tumor response (40).

All patients treated in the study must have at least one measurable lesion for inclusion according to RECIST v1.1 (see Section 7.2 Inclusion Criteria I 08).

Tumor assessment (either CT scan or magnetic resonance imaging [MRI]) will be performed to assess disease status at baseline and then every 8 weeks from Cycle 1 Day 1 with flexibility of +/- 7 days, approximately corresponding to the even-numbered cycles.

Antitumoral response information, ie, category of response such as CR, PR, SD as best response, or progressive disease, will be determined by the Investigator in patients with evaluable disease (RECIST v1.1, [Appendix C]). Furthermore, a PR or a CR must be confirmed on a second examination done at least 4 weeks apart, in order to confirm the antitumoral response. In addition to investigator's/local radiologist's assessments, copies of all imaging sets will be systematically collected for the purpose of ICR in Part B only (refer to specific imaging charter and manual).

10 PATIENT SAFETY (ALL STUDY PARTS)

10.1 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

Refer to Section 9.1 for definition of safety criteria, parameters to be analyzed and method of sample collection.

10.2 SAFETY INSTRUCTIONS

Please refer to Section 6.7.

10.3 ADVERSE EVENTS MONITORING

All AEs will be managed and reported in compliance with all applicable regulations and included in the final CSR.

10.4 DEFINITIONS OF ADVERSE EVENT AND SERIOUS ADVERSE EVENT

An **adverse event** is any untoward medical occurrence in a patient or clinical investigation patient administered with a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A **serious adverse event** is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;

  Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event:

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Note: Examples of such events (list is not exhaustive) are intensive treatment in an emergency room or at home (for allergic bronchospasm, blood dyscrasias, or convulsions) or asymptomatic ALT increase ≥10 x ULN that does not result in hospitalization, or development of drug dependency or drug abuse.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 Adverse events

All AEs regardless of seriousness or relationship to the study treatment, spanning from the signature of the ICF (ie, occurring during the baseline period even in the absence of any administration of study treatment), up to 30 days following the last administration of study treatment, are to be recorded on the corresponding page(s) included in the eCRF.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to study treatment, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study treatment.

Vital signs or electrocardiogram (ECG) abnormalities are to be recorded as AEs only if they are symptomatic and/or requiring corrective treatment and/or leading to treatment discontinuation and/or modification of dosing and/or fulfilling a seriousness criterion and/or is defined as an AESI (see Section 10.5.5).

Laboratory abnormalities are to be recorded as AEs only if they lead to treatment discontinuation and/or modification of dosing and/or fulfill a seriousness criterion and/or are defined as an AESI (see Section 10.5.5).

10.5.2 Serious adverse events

In the case of a SAE, an AESI, a pregnancy report, or an overdose, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screen of the eCRF; the system will automatically send e-notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In such cases, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medication, patient status) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge. In addition, any effort should be made to further document each SAE that is fatal or life threatening within the week (7 days) following initial notification.
- A back-up plan is used (using paper flow) when the eCRF system does not work.

10.5.3 Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any AEs (clinical signs, laboratory values or other, etc) until the return to normal or consolidation of the patient's condition. Ongoing related AEs at the end of study treatment will be followed until resolution or stabilization.
- In case of any SAE/AESI, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until outcome has been stabilized. This may imply that follow-up may continue after the patient has discontinued study treatment or has left the clinical trial and that additional investigations may be requested by the monitoring team.
- In case of any AE or AESI brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the study treatment with a reasonable possibility, should be reported to the monitoring team.

10.5.4 Treatment discontinuation due to nonserious adverse event

In the case of a treatment discontinuation due to a nonserious AE:

- ENTER (within 24 hours) the information related to treatment discontinuation due to a non-SAE in the appropriate screen of the eCRF (AE with the box “action taken with study treatment” ticked “permanently discontinued”, together with the EOT form with reason that should be ticked “AE”); the system will automatically send the notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.

10.5.5 Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor’s product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

Study treatment-related DLTs (as defined in Section 9.1.1) are considered as AESIs, and as such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of the event. The Investigator will attach the DLT-specific CRF page to the DLT/AESI form.

AESIs in this study are:

- Pregnancy of a female subject entered in a study.
  - Pregnancy occurring in a female patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4).
  - In the event of pregnancy in a female participant, study treatment should be discontinued.
  - Follow-up of the pregnancy in a female participant is mandatory until the outcome has been determined.

- Symptomatic overdose with study treatment (serious or nonserious)
  - An overdose (accidental or intentional) with the study treatment is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.

    Symptomatic overdose has to be reported to the Sponsor immediately (within 24 hours).
- Grade ≥3 Increase of ALT (Alanine Amino -Transferase)
  - LFTs include AST, ALT, ALP (isoenzymes if grade >2), total bilirubin (fractionated if >2 x ULN direct), GGT, and INR (if total bilirubin >2.5 ULN).
  - Omit study-treatment and repeat LFTs within 2-3 days. If not recovered, monitor LFTs weekly until recovery to Grade ≤1 (or baseline grade) (refer to Dose modification Section 6.5. section of the appropriate study arm)
  - Confounding factors such as, liver metastasis, hepato-biliary disorders, concomitant medications, etc. should be excluded prior to dose modifications.
  - Close monitoring of study patients is recommended in cases of increase of Grade ≥3 ALT. The LFTs should be performed in patients with onset of otherwise unexplained nausea, jaundice, right upper abdominal pain, fever, or rash.
  - An ultrasound, or other imaging of liver, should be considered based on the clinical presentation.
  - A consultation with hepatologist should be undertaken if there is:
    - Unexplained or persistent Grade ≥3 ALT regardless of the dose omissions
    - ALT Grade >3 ULN and concomitant jaundice (total bilirubin Grade >2.5 ULN), in patients with normal ALT and total bilirubin at baseline
    - To exclude hepato-biliary disorders (eg, hepatotropic virus infections, autoimmune or alcoholic hepatitis, Non-Alcoholic Steatohepatitis, etc.) or drug induced liver injury
  - Further hepatic virology will be undertaken as per the site's local guidelines for the treatment of cancer patients, considering the local and national recommendations
- Photosensitivity
  - If photosensitivity is suspected in study participants, consider dermatologist consultation. Confounding factors such as other dermatological disorders, drug eruptions resulting from concomitant medication use, etc. should be excluded prior to any dose modification. In case of study intervention discontinuation because of photosensitivity reaction, study participant should be followed for possibility of development of other manifestations of photosensitivity such as photo-onycholysis, lichenoid reaction or actinic granuloma.

10.5.6 Laboratory abnormalities

Laboratory abnormalities should be monitored, documented, and managed according to the related flowchart (see Section 1.3). Laboratory values will be reported in the appropriate screen of eCRF.

Laboratory abnormalities should be reported as AEs only in case they lead to an action on study treatment or if they fulfil the criteria for seriousness or if they are DLTs/AESIs (see Section 10.5.1).

10.6 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are unexpected and are at least reasonably related to the study treatment (ie, suspected unexpected serious adverse reactions), to the regulatory authorities, Institutional Ethics Committees (IECs)/Institutional Review Boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the study treatment to the regulatory authorities, according to local regulations.
- The AESIs (ie, DLT, pregnancy, overdose, ALT ≥ Grade 3, photosensitivity) to those regulatory authorities who require such reporting.

Adverse events that are considered expected will be specified by the reference safety information (Investigator's Brochure).

The Sponsor will report all safety observations made during the conduct of the trial in the CSR.

11 HANDLING OF PATIENT TEMPORARY AND PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

Pregnancy will lead to definitive treatment discontinuation in all cases.

11.1 PERMANENT TREATMENT DISCONTINUATION WITH INVESTIGATIONAL MEDICINAL PRODUCT(S)

11.1.1 List of criteria for permanent treatment discontinuation

Patients may withdraw from study treatment if they decide to do so, at any time and irrespective of the reason, or this may be done at the discretion of the Investigator. All efforts should be made to document the reason(s) for discontinuation, and this should be documented in the eCRF.

In Arms #2, #3, #4, and #5 (Parts C/D, F/G, H/I and J/K), Palbociclib / alpelisib / everolimus / abemaciclib can be prematurely discontinued; in that case, amcenestrant can be continued as a monotherapy until the EOT criterion is met. The EOT visit in this case will be 30 days after the date of last amcenestrant administration. The reason for premature discontinuation will be captured in the appropriate eCRF screen.

Treatment with the study treatment should be discontinued in any of the following cases:

- At the patient's request, at any time and irrespective of the reason (consent's withdrawal), or at the request of their legally authorized representative. "Legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for nonpatient contact follow-up, eg, medical records check. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study. Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document any case of withdrawal of consent.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the patient's wellbeing, such as:
  - Disease progression
  - Unacceptable AE
  - Poor compliance to the study protocol
  - Any other reason such as intercurrent illness that prevents further administration of study treatment (will be specified).
- Patient is lost to follow-up.

If patients are clinically stable, and possibly deriving clinical benefit from therapy with minimal toxicity, the patient will be maintained on treatment for the maximum period of time defined in Section 6.8.

11.1.2 Handling of patients after permanent treatment discontinuation

All permanent study treatment discontinuation must be recorded by the Investigator in the appropriate screen of eCRF when considered as confirmed. After study treatment is discontinued, patients should complete a visit 30 days after the last administration of the study treatment or before other anti-cancer therapy initiation, whichever occurs first as described in Section 12.7.

Patients who have been withdrawn from the study treatment cannot be re-entered in any other part of the study.

11.2 REPLACEMENT OF PATIENTS

During the dose escalation part of the study, a patient may be considered not evaluable for DLT and may be replaced at the same dose level as described in Section 6.3.

Patients treated in the expansion part of the study who are withdrawn from study treatment will not be replaced.

11.3 CRITERIA FOR TEMPORARILY DELAYING

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Appendix J should be considered.

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

During the course of the study, all patients entering the study must be evaluated according to the schedule outlined in the flow charts in Section 1 and described below. The results of the evaluation will be recorded in the eCRF pages until the patient is not followed anymore.

After the baseline visit, all eligible patients included in the study will return to the site for a study visit every week during Cycle 1 and 2, every 2 weeks from Cycle 3 to Cycle 6 (inclusive), and once a month from Cycle 7 onwards. A final visit will be performed 30 days after the last administration of the study treatment corresponding to the EOT visit (see flow chart for investigations to be performed).

The patients will be followed until recovery or consolidation of any SAE or study treatment-related AE.

Patients who discontinue the study treatment prior to documentation of disease progression will be followed-up every 2 months until disease progression or initiation of further anti-cancer therapy, or COD, whichever comes first.

12.2 BASELINE EVALUATION

The pretreatment examinations are to be performed within 28 days prior to the first administration of the study treatment, unless otherwise specified below.

The study (main) ICF (mandatory) and optional pharmacogenetics ICF (if applicable) will have to be signed by the patient before any procedure specific to the study can be performed. The following assessments are to be performed at this visit.
For **Arm #3** (Parts F and G) only, for eligibility purposes, a *PIK3CA* Testing ICF will have to be signed prior to the *PIK3CA* test for patients who have never had this test done to confirm/detect the *PIK3CA* mutation that is necessary for treatment with amcenestrant and alpelisib combination. Upon signing the *PIK3CA* Testing ICF (ie, pre-screening), the test should be performed prior to the study main ICF is signed and initiation of any screening procedure (ie, any time before the 28-day screening period). No fresh biopsy will be required from Sponsor for eligibility purposes. All PIK3CA reports regardless of the time of testing (recent/archival) are acceptable.

- Breast cancer diagnosis and history.
- Prior breast anticancer therapies.
- Prior medications use from the date of informed consent.
- Tumoral evaluation: chest, abdomen and pelvis CT or MRI scan. Throughout the course of the study the same techniques for imaging evaluation than the ones used during the baseline phase should be used.
- Preferably fresh tumor biopsy or archived tumor samples (within past 3 months prior to study treatment initiation) for patients who consent for paired biopsies (prior and during treatment) and with accessible tumor. Biopsy is optional for patients in Arm #1 Part B (in

at least 10 patients) and Arm #3 Parts F/G and mandatory for all patients in Arm #1 Part A. Access to tissue FFPE blocks for IHC and RNA analysis is the preferred option. Alternatively, approximately 9 FFPE slides will be collected for central IHC and 3 FFPE slides for RNA analysis.

The following will be performed within 7 days prior to Day 1:

- Inclusion/exclusion criteria.
- Clinical examination including: major body system examination, ECOG performance status (Appendix A), height, weight, vital signs (body temperature, blood pressure, heart rate, respiration rate) and signs and symptoms.
- Laboratory assessments:
  - Hematology: hemoglobin, white blood cell count with differential, platelet count
  - Coagulation: international normalized ratio, prothrombin time
    - Arm #3 Part F and G only: activated Partial Thromboplastin Time (aPTT) done in addition to INR and PT
  - Blood chemistry:
    - Liver function tests: AST, ALT, total bilirubin, conjugated bilirubin, ALP, GGT.
    - Electrolytes: sodium, potassium, chloride, magnesium, calcium, phosphate, bicarbonate or BUN
    - Serum Albumin
    - Renal function tests: creatinine
    - **Arm #3 and #4 (Part F, G, H and I) only: FPG, HbA1c**
    - Arm #4 (Parts H and I): lipid panel, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides and total cholesterol
    - Additional tests to be performed when clinically appropriate.
- Urine analysis on morning spot: dipstick or qualitative analysis for pH, glucose, ketones, blood, protein and leucocytes. A 24-hour urine collection may be done for determination of proteinuria if 3+ protein on dipstick.
- 12-lead ECG.
- Arm #1 Part A only: ^{18}F-FES-PET scan (Part A QD and BID) and FDG PET/CT (Part A BID) 3 days or more before the first dose of study treatment).

The procedures described above are not to be repeated before study treatment administration for Cycle 1, provided they were performed during the baseline process, within 7 days of the start of administration and that they did not show significant abnormalities.

All patients who signed the study ICF will be assigned a patient number. Each patient will receive an incremental identification number per site corresponding to their order of enrollment in the study. Those patients, who meet all the inclusion criteria and none of the exclusion criteria, will be eligible for registration in the study.

12.3 BEFORE THE FIRST INVESTIGATIONAL MEDICINAL PRODUCT ADMINISTRATION (WITHIN 2 DAYS BEFORE) IF NOT PERFORMED WITHIN THE 7 PREVIOUS DAYS

Before Cycle 1, evaluations such as vital signs, body weight, ECOG performance status, signs and symptoms, physical examination, ECG, hematology, coagulation, chemistry and urinalysis should be repeated within 2 days before the study treatment administration if abnormal or performed more than 7 days before study treatment administration.

12.4 DURING THE TREATMENT PERIOD AT CYCLE 1

See flow charts in Section 1.3 and Section 1.4.

Assessments should be performed when possible prior to administration of study treatment unless otherwise indicated. Results should be reviewed by the Investigator. Every effort should be made to keep the schedule of assessments on time for each patient. All visits should be performed on the day specified, unless otherwise noted. Additional safety tests (eg, ECG) can be performed whenever clinically indicated. All the tests or procedures on Day 1 should be done at predose time unless otherwise stated.

12.4.1 Cycle 1, Day 1

In Arms #1, #2, #4, #5 (Parts A, B, C, D, H, I, J and K), Cycle 1 Day 1 corresponds to the first administration of amcenestrant or amcenestrant combined with palbociclib (Arm #2 Parts C and D) / everolimus (Arm #4 Parts H and I)/abemaciclib (Arm #5 Parts J and K). The drug(s) will be administered at the study site at each protocol-defined visit. Other doses will be self-administered daily.

In Arm #3 Parts F and G, Cycle 1 Day 1 corresponds to the first administration of alpelisib alone. Alpelisib PK sampling will be done on Cycle 1 Day 3 (ie, on the third day after the start of alpelisib administration).

The day on which the patient receives the initial dose of study medication is referred as Cycle 1 Day 1 (Day 1 of the study). The examinations described in Section 12.2 are not to be repeated for Cycle 1, provided they were performed within 7 days of the start of study treatment and provided that they did not show significant abnormalities.

- PK/PD blood sample collection are collected at different time points and are detailed in the PK/PD flow chart (Section 1.4)

12.4.2 Cycle 1, Day 3

- PK/PD blood sample collection collected at different time points, detailed in the PK/PD flow chart (Section 1.4).
- Patient diary review

12.4.3 Cycle 1, Day 8 (±1 day)

- Physical examination, vital signs (temperature, blood pressure, heart rate, respiration rate)
- Laboratory assessments: hematology and blood chemistry.
- All AEs/SAEs throughout the cycle.
- Concomitant medications.
- PK/PD blood sample collection collected predose, as detailed in the PK/PD flow chart (Section 1.4).
- Patient diary review

12.4.4 Cycle 1, between Day 11 and Day 15 (Arm #1 Part A only)

- Part A only: ^{18}F-FES-PET scan (all Part A QD and BID patients) and FDG PET/CT (Part A BID only)
- PK/PD blood sample collection as detailed in the PK/PD flow chart (Section 1.4).
- Patient diary review

12.4.5 Cycle 1, Day 15 (±2 days)

- Physical examination, ECOG performance status (Appendix A), weight, vital signs (temperature, blood pressure, heart rate, respiration rate).
- Laboratory assessments: hematology, coagulation, and blood chemistry.
- Urine analysis: dipstick on morning spot.
- All AEs/SAEs throughout the cycle.
- Concomitant medications.
- PK/PD blood sample collection collected at different time points, detailed in the PK/PD flow chart (Section 1.4).
- Patient diary review.

12.4.6 Cycle 1, Day 22 (±2 days)

Note, for Arm #2 Parts C and D, the following assessments should be performed on Day 21.

- Physical examination, vital signs (temperature, blood pressure, heart rate, respiration rate).
- Laboratory assessments: hematology and blood chemistry.
- All AEs/SAEs throughout the cycle.
- Concomitant medications.
- PK/PD blood sample collection collected at different time points, detailed in the PK/PD flow chart (Section 1.4).
- Patient diary review

12.5 DURING SUBSEQUENT CYCLES

See flow charts in Section 1.3 and Section 1.4.

12.5.1 Subsequent cycles, Day 1 (±2 days)

- Physical examination, ECOG performance status (Appendix A), weight, vital signs (temperature, blood pressure, heart rate, respiration rate).
- Laboratory assessments: hematology, coagulation, and blood chemistry.
- Urine analysis: dipstick on morning spot.
- 12-lead ECG.
- All AEs/SAEs throughout the cycle.
- Concomitant medications.
- PK/PD blood sample collection collected in Cycle 2 only, detailed in the PK/PD flow chart (Section 1.4).
- Patient diary review.

12.5.2 Cycle 2, Day 8 (±2 days)

- Physical examination, vital signs (temperature, blood pressure, heart rate, respiration rate).
- Laboratory assessments: hematology and blood chemistry.
- All AEs/SAEs throughout the cycle.
- Concomitant medications.
- Patient diary review.

12.5.3 Cycle 2, Day 15 (±2 days)

- Physical examination, ECOG performance status (Appendix A), weight, vital signs (temperature, blood pressure, heart rate, respiration rate).
- Laboratory assessments: hematology, coagulation, and blood chemistry.
- Urine analysis: dipstick on morning spot.
- All AEs/SAEs throughout the cycle.
- Concomitant medications.
- Patient diary review.

12.5.4 Cycle 2, Day 22 (±2 days)

- Physical examination, vital signs (temperature, blood pressure, heart rate, respiration rate).
- Laboratory assessments: hematology and blood chemistry.
- All AEs/SAEs throughout the cycle.
- Concomitant medications.
- At the end of Cycle 2, between D15 to D28, tumor biopsy for patients who consent for paired biopsies and with accessible tumor, (optional in at least 10 patients in Part B and mandatory for Part A).

- At the end of Cycle 2, between D15 to D28, blood sample for ESR1 mutation status.
- Patient diary review.

12.5.5 Subsequent cycles (up to and including C6), Day 15 (±2 days)

- Physical examination, ECOG performance status (Appendix A), weight, vital signs (temperature, blood pressure, heart rate, respiration rate).
- Laboratory assessments: hematology, coagulation, and blood chemistry.
- Urine analysis: dipstick on morning spot.
- All AEs/SAEs throughout the cycle.
- Concomitant medications.
- Patient diary review.

12.5.6 Subsequent cycles (starting from C7 and onwards), Day 1 (±2 days)

- Physical examination, ECOG performance status (Appendix A), weight, vital signs (temperature, blood pressure, heart rate, respiration rate).
- Laboratory assessments: hematology, coagulation, and blood chemistry.
- Urine analysis: dipstick on morning spot.
- All AEs/SAEs throughout the cycle.
- Concomitant medications.
- Patient diary review.

12.5.6.1 Every 8 weeks

- Tumoral evaluation: chest, abdomen and pelvis CT only or MRI scan only (whichever was used at baseline). Either one of the exams is to be performed every 8 weeks from Cycle 1 Day 1 with flexibility of +/- 7 days, approximately corresponding to the even-numbered cycles starting at Cycle 2, or when clinically indicated during study treatment, whenever disease progression is suspected, or to confirm a PR or CR (at least 4 weeks after documentation of response). To ensure comparability, the imaging should be performed ***using identical radiology techniques*** throughout the study treatment period (ie, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and the same scanner).
- PK/PD blood sample collection collected in Cycle 2, 4 and 6 only, detailed in the PK/PD flow chart (Section 1.4).

12.5.6.2 Additional Tests for Arms #3 and #4 (Parts F, G, H, and I)

FPG and HbA1C monitoring will be in Arm #3 and #4 only:

- *Fasting Serum Glucose* sample for safety assessment will be collected after 8-12 hours of an overnight fasting prior to the light breakfast, at the following time points:
  - Baseline (in the screening period): approximately 2 weeks, and no later than Day-1 prior to study treatment (C1D1)
  - Cycle 1: Day 8 and Day 15
  - Cycle 2: Day 1, Day 15, and Day 28
  - Subsequent cycles: Day 1
  - EOT
  - As clinically indicated
- *Hemoglobin A1C (HbA1C)* will be assessed for safety, after 8-12 hours of an overnight fasting, pre-dose prior to the light breakfast, at the following time points:
  - Baseline (in the screening period): approximately 2 weeks, and no later than Day-1 prior to study treatment (C1D1)
  - Cycle 1 and Cycle 2 Day 1, and thereafter, on every 3rd cycle Day 1 (ie, C5D1, C8D1 etc.)
  - EOT
  - As clinically indicated

12.6 END OF TREATMENT VISIT (TO BE PERFORMED BETWEEN 22 AND 30 DAYS AFTER THE LAST ADMINISTRATION OF THE STUDY TREATMENT)

All patients must continue to be observed for at least 22 to 30 days after the final dose of study treatment or prior to start of further anticancer therapy, whichever comes first. The following procedures should be performed approximately 30 days following the final dose of study treatment:

- ECOG performance status (Appendix A), weight, physical examination, vital signs (temperature, blood pressure, heart rate, respiration rate).
- Laboratory assessments:
  - Hematology
  - Coagulation
    - Arm #3 Part F and G only: activated partial thromboplastin time (aPTT) done in addition to INR and PT
  - Blood chemistry
    - Arm #3 and #4 (Part F, G, H and I) only: FPG, HbA1c
    - Arm #4 (Parts H and I) only: lipid panel
- Urine analysis: dipstick on morning spot.
- 12-lead ECG.

- AE collection to 30 days after the last administration of study treatment (will be collected in last treatment cycle). Ongoing SAEs and ongoing related AEs should be followed beyond EOT until resolution or stabilization.
- Concomitant medications to be collected up to 30 days from last study treatment administration and after the EOT if associated with an ongoing SAE or ongoing related AE.
- Tumoral evaluation: chest, abdomen and pelvis CT or MRI scan (whichever was used at baseline) unless already performed at previous cycle.
- Blood samples for molecular profiling in cfDNA (NGS, plasma).

In case the EOT visit is performed before Day 22 due to the initiation of the further anti-cancer therapy, the final collection of safety information (stabilization or recovery of TEAEs) should be done either as phone call or visit on/around Day 30 as per protocol allowed window.

12.7 PERIOD POST END OF TREATMENT

Follow up will be performed for patients with ongoing SAEs regardless of relationship to study treatment and ongoing study treatment-related AEs 30 days after the last study treatment administration, and for patients with new study treatment-related AEs/SAEs. Those events will be followed until resolution or stabilization as described in Section 10.5.3 and Section 11.1.2.
Follow up will be performed for patients who discontinued study treatment without disease progression (for reasons: the post-treatment follow-up period includes either telephone calls or visits every 2 months to collect date of disease progression or date of further anticancer therapy (whichever occurs first).

12.8 POST STUDY CUT-OFF PERIOD

If a patient continues to benefit from the treatment after the final study COD, the patient can continue study treatment. Such patients will be followed until 30 days after the last administration of the study treatment and will continue to undergo selected study assessments. After the final study COD, ongoing patients will receive study therapy until disease progression, occurrence of unacceptable toxicities, whichever is earlier, and they will only be followed for study treatment administration, SAEs, study treatment-related AEs and AEs leading to study treatment discontinuation.

13 STATISTICAL CONSIDERATIONS

The content of this section is the Statistical Analysis Plan for the study.

13.1 DETERMINATION OF SAMPLE SIZE

A total of up to approximately 251 patients may be enrolled in this study, in all treatment arms overall. The study will be conducted in the European Union, United States and Canada.

13.2 ARM #1

13.2.1 Sample size of the escalation phase for amcenestrant as monotherapy (Part A)

This study aims to establish the MTD as well as the RD of amcenestrant according to DLTs observed.

The actual sample size is expected to vary depending on DLTs observed, cohort sizes and number of dose levels. It is anticipated that around 31 to 42 evaluable patients will be enrolled in the escalation part (Part A).

13.2.2 Sample size of the expansion phase for amcenestrant as monotherapy (Part B)

In case of a QD administration, a Simon's 2-stage design (minimax) will be used. If 4 or fewer responses (CR + PR) are observed on the first 45 patients evaluable for response, the alternative hypothesis of at least a 20% response rate will be rejected. Otherwise, accrual will continue to the full sample size of 78 patients. Overall, this procedure has 80% statistical power (1-sided alpha of 0.05) to reject a null response rate of 10% in a 1-sample test for a binomial proportion (East version 6.3, Cytel Software, Cambridge, MA). Thirteen responses on 78 evaluable patients for response will be necessary to reject the null hypothesis.

13.3 ARM #2

13.3.1 Sample size of the escalation phase for amcenestrant in combination with palbociclib (Part C)

This study aims to establish the MTD of amcenestrant in combination with palbociclib according to DLTs observed.

The actual sample size is expected to vary depending on DLTs observed and number of dose levels. The study will follow a standard 3 + 3 design evaluating escalating dose levels of amcenestrant in combination with palbociclib.

For the dose escalation phase (Part C) it is anticipated that approximately 12 patients will be enrolled depending on the DLTs observed.

13.3.2 Sample size of the expansion phase for amcenestrant in combination with palbociclib (Part D)

It is anticipated that approximately 28 patients will be treated in an expansion phase at each selected RD of amcenestrant in combination with palbociclib in order to further assess the safety, tolerability and PK profiles and to explore preliminary antitumoral activity.

With a sample size of 28 patients, there is a 76% probability of detecting a safety event with a true incidence of 5%.

Safety event incidence rate	Number of patients				
	12	24	28	40	56
1%	0.11	0.21	0.25	0.33	0.43
2.5%	0.26	0.46	0.51	0.64	0.76
5%	0.46	0.71	0.76	0.87	0.94
10%	0.72	0.92	0.95	0.99	1.00
15%	0.86	0.98	0.99	1.00	1.00

13.4 ARM #3

13.4.1 Sample size of the safety run-in part for amcenestrant in combination with alpelisib (Part F)

This part of the study aims to confirm the RD of amcenestrant in combination with alpelisib according to DLTs observed.

The actual sample size is expected to vary depending on DLTs observed and number of dose levels. This part of the study will follow the decision tree in Section 6.2.1 to assess the combination of amcenestrant with alpelisib. Additional patients may be enrolled to better evaluate the PK profile of each drug.

It is anticipated that approximately 6 patients will be enrolled depending on the DLTs observed and tested doses.

13.4.2 Sample size of the expansion phase for amcenestrant in combination with alpelisib (Part G)

It is anticipated that approximately 34 patients will be treated in an expansion phase at the selected RD of amcenestrant in combination with alpelisib in order to further assess the safety, tolerability, PK profiles for preliminary exploration of antitumoral activity.

With a sample size of 34 patients, there is an 83% probability of detecting a safety event with a true incidence of 5%.

Safety event incidence rate	Number of patients				
	12	24	28	34	40
1%	0.11	0.21	0.25	0.29	0.33
2.5%	0.26	0.46	0.51	0.58	0.64
5%	0.46	0.71	0.76	0.83	0.87
10%	0.72	0.92	0.95	0.97	0.99
15%	0.86	0.98	0.99	1.00	1.00

13.5 ARM #4

13.5.1 Sample size of the dose escalation part for amcenestrant in combination with everolimus (Part H)

This part of the study aims to confirm the RD of amcenestrant in combination with everolimus according to DLTs observed.

The actual sample size is expected to vary depending on DLTs observed and number of dose levels. This part of the study will follow the decision tree in Section 6.2.1 to assess the combination of amcenestrant with everolimus. Additional patients may be enrolled to better evaluate the PK profile of each drug.

It is anticipated that approximately 12 patients will be enrolled depending on the DLTs observed and tested doses.

13.5.2 Sample size of the expansion phase for amcenestrant in combination with everolimus (Part I)

It is anticipated that approximately 12 patients will be treated in an expansion phase at each selected RD of amcenestrant in combination with everolimus in order to further assess the safety, tolerability and PK profiles and to explore preliminary antitumoral activity.

With a sample size of 12 patients, there is a 72% probability of detecting a safety event with a true incidence of 10%.

Safety event incidence rate	Number of patients			
	6	12	15	18
1%	0.06	0.11	0.140.	0.17
2.5%	0.14	0.26	0.32	0.37
5%	0.27	0.46	0.54	0.60
10%	0.47	0.72	0.79	0.85
15%	0.62	0.86	0.91	0.95

13.6 ARM #5

13.6.1 Sample size of the dose escalation part for amcenestrant in combination with abemaciclib (Part J)

This part of the study aims to confirm the RD of amcenestrant in combination with abemaciclib according to DLTs observed.

The actual sample size is expected to vary depending on DLTs observed and number of dose levels. This part of the study will follow the decision tree in Section 6.2.1 to assess the combination of amcenestrant with abemaciclib. Additional patients may be enrolled to better evaluate the PK profile of each drug. It is anticipated that approximately 12 patients will be enrolled depending on the DLTs observed and tested doses.

13.6.2 Sample size of the expansion phase for amcenestrant in combination with abemaciclib (Part K)

It is anticipated that approximately 20 patients will be treated in an expansion phase at each selected RD of amcenestrant in combination with abemaciclib in order to further assess the safety, tolerability and PK profiles and to explore preliminary antitumoral activity.

With a sample size of 20 patients, there is a 71% probability of detecting a safety event with a true incidence of 5%.

Safety event incidence rate	Number of patients			
	6	20	23	26
1%	0.06	0.21	0.21	0.23
2.5%	0.14	0.46	0.44	0.48
5%	0.27	0.71	0.69	0.74
10%	0.47	0.92	0.91	0.94
15%	0.62	0.98	0.98	0.99

13.7 PATIENT DESCRIPTION

Dose escalation of monotherapy Arms #1 (Part A), dose escalation monotherapy Arm #1 (Part B) dose escalation combination Arm #2 (Part C), dose expansion combination Arm #2, #3, #4, and #5 (Parts D, G, I, K), safety run-in combination Arm #3 (Part F), dose escalation combination Arm #4 and #5 (Parts H and J) results will be displayed separately. Pooled analysis for a given treatment could be considered (eg, Arm #1 Part A and B).

13.7.1 Disposition of patients

Disposition of patients will be depicted by intended dose level (including expanded cohort) for both the patient study status and also for the patient analysis populations. For patient study status, the total number of patients for each one of the following categories will be presented in the CSR using a flow-chart diagram or summary table:

- Registered patients are patients who sign the study informed consent, and who plan to receive the study treatment.
- All-treated/safety population.
- Patients who complete the study treatment period.
- Patients who discontinue study treatment and reasons for discontinuation.
- Patients evaluable for DLT assessment.
- PK population.
- PD population.
- Activity/efficacy population.

For all categories of patients, percentages will be calculated using the number of exposed patients (all-treated population). Reasons for treatment discontinuation will be provided in tables giving numbers and percentages by dose level.

Additionally, the analysis populations for safety, efficacy, PK, and PD will be summarized in a table by patient counts for the all-treated population.

13.7.2 Protocol deviations

Major protocol deviations which compromise the evaluation of the MTD will be derived adequately (mainly algorithmically and/or following medical review) and determination of deviations will be finalized based on data review conducted prior to database lock. Decisions made on a patient's status will be documented.

13.8 ANALYSIS POPULATIONS

13.8.1 All-treated/safety population

The all-treated/safety population is defined as all registered patients exposed to the study treatment, regardless of the amount of treatment administered.

13.8.2 Patients evaluable for DLT assessment

To be evaluable, patients should have received 1 cycle (28 days, oral administration), with intake of at least 75% of the intended doses, unless they discontinued study treatment before Cycle 1 completion due to a DLT (a patient who discontinues the study treatment before the end of Cycle 1 for another reason than DLT will be replaced), and in Part A have an evaluable

^{18}F-FES-PET scan at baseline and between Days 11 and 15 of the first cycle. Any patient who develops a DLT in Part A despite the absence of evaluable ^{18}F-FES-PET scan will be included in the DLT population.

A complete safety evaluation should be performed during Cycle 1, and a DLT form should be completed at the end of the cycle. This concerns both patients followed up to the end of the evaluation period and patients who experience a DLT validated by the Study Committee. Patients with incomplete safety evaluation during Cycle 1 and who experience a DLT at this cycle will be considered as evaluable for DLT.

Patients who are not evaluable for DLT assessment in the dose escalation part will be replaced.

13.8.3 Pharmacokinetic population

The PK analysis will be performed on patients having received at least 1 cycle of study treatment, without any major deviations related to study treatment administration (eg, early vomiting just after administration), and for whom any PK parameter can be derived. In order to derive PK parameters, the corresponding dosing information (time and amount) and sampling information (time) must be recorded.

13.8.4 Activity/efficacy population

The activity/efficacy population (called response-evaluable population) is defined as all treated patients with measurable disease at study entry who provided a baseline and at least one postbaseline evaluable tumor assessment. Patients with an early progression as per RECIST v1.1, or who died from disease progression will also be included in this set.

13.8.5 Pharmacodynamic population

PD analyses will be performed on all treated patients who had an evaluable ^{18}F-FES-PET scan at baseline and between Days 11 and 15 of Cycle 1 for Arm #1 Part A only.

13.9 STATISTICAL METHODS

Unless otherwise specified, analyses will be descriptive and performed based on the all-treated population.

Continuous data will be summarized using number of available data, mean, standard deviation, median, minimum and maximum for each dose level. Categorical and ordinal data will be summarized using number and percentage of patients in each dose level.

13.9.1 Demographics and baseline characteristics

Standard demographic and baseline characteristics (including age, race, gender, ECOG performance status), medical history, cancer diagnosis, and tumor characteristics will be collected at baseline and described by dose level.

The following parameters regarding prior anticancer therapy will be summarized:

- For surgery and radiotherapy: time from last procedure to first intake of study treatment.
- For chemotherapy, gene therapy, immunotherapy, hormonal therapy, targeted therapy: time from last administration to first intake of study treatment.

Parameters will be summarized by dose level and overall using descriptive statistics.

13.9.2 Extent of investigational medicinal product exposure

The extent of study treatment exposure will be assessed and summarized by dose level within the all-treated population.

In addition, dose information will be assessed for the following variables:

- Cumulative dose for amcenestrant, palbociclib, alpelisib, everolimus and abemaciclib: eg, the cumulative dose at Cycle K is the sum of all doses from Cycle 1 to and including Cycle K.
- Actual dose intensity for amcenestrant, palbociclib, alpelisib, everolimus and abemaciclib is defined as the cumulative dose divided by the number of weeks on study treatment.
- Relative dose intensity for amcenestrant, palbociclib, alpelisib, everolimus and abemaciclib is defined as the ratio of the actual dose intensity to the planned dose intensity. The relative dose intensity is an indicator of the feasibility of the chosen schedule of administration.
- Dose reduction: reduction of the administered amcenestrant, palbociclib, alpelisib, everolimus and abemaciclib dose at an intake on day n + 1 compared to the previous intake on day n or the day before dose(s) omitted.
- Dose omission: one omission of an amcenestrant, palbociclib, alpelisib, everolimus or abemaciclib dose corresponds to a dose with a dose equal to 0 mg/day. Omission can occur within cycle n or Cycle n +1.
- Cycle delays (Arms #2, #3, #4 and #5): A cycle is deemed to have been delayed if start date of the current cycle - start date of previous cycle >31 days (28 +3 days).
- Partially administered cycle: cycle with at least one dose omitted.

Dose information variables will be summarized descriptively (n, mean, standard deviation, median, minimum, and maximum). Analyses will be performed based on the number of patients and on the number of cycles.

13.9.3 Prior/concomitant medication/therapy

Medications will be summarized by treatment group according to the World Health Organization Drug Dictionary, considering the first digit of the anatomical, therapeutic, and chemical (ATC) class (anatomic category) and the first three digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized patients will be counted once in each ATC categories (anatomic or therapeutic) linked to the medication.

Medications of specific interest such as antibiotics and hematopoietic growth factors (granulocyte-colony stimulating factor, granulocyte macrophage colony stimulating factor and erythropoietin or red blood cells transfusion) will be summarized and listed by dose level.

Further treatment of interest for the analysis and given to the patient after withdrawal from study treatment will be listed.

13.9.4 Analyses of safety data

13.9.4.1 Dose-limiting toxicities

The DLTs observed during DLT observation period will be summarized on the DLT-evaluable population, by dose level. In addition, AEs that meet the DLT criteria in subsequent cycles will be summarized on the safety population. Details will be provided (characteristics of DLTs) by patient.

13.9.4.2 Analyses of adverse events

Adverse events will be collected from the time informed consent is signed until at least 30 days after the last administration of the study treatment and will be categorized according to NCI-CTCAE v4.03. All AEs will be classified by system organ class and preferred term according to the latest available version of the MedDRA dictionary.

Definitions

Period of observation: The observation period will be divided into 3 segments: pretreatment, on-treatment, and posttreatment. The pretreatment period is defined as the time from when the patients give informed consent and the first administration of the study treatment. The on-treatment period is defined as the time from the first dose of study treatment up to 30 days after the last dose of study treatment. The posttreatment period is defined as the time starting 31 days after the last dose of study treatment to the study closure.

Pretreatment AEs are defined as any AE occurring during the pretreatment period.

Treatment-emergent AEs are defined as AEs that developed or worsened (according to the Investigator’s opinion) or became serious during the on-treatment phase.

Post-treatment AEs are defined as AEs that are reported during the posttreatment period.

The NCI-CTCAE v.4.03 grade will be provided in the summary. For patients with multiple occurrences of the same preferred term, the maximum grade will be used.

The primary focus of AE reporting will be the TEAEs. Pre and posttreatment AEs will be described separately.

Adverse event incidence tables will be presented for each dose level, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the all treated population within each dose level.

Sorting within tables should ensure the same presentation for the set of all AE within the observation period (pre, on-, and posttreatment). For that purpose, the table of all TEAEs presented by system organ class and preferred term will be sorted by internationally agreed order, unless otherwise specified. Full 4-level hierarchy will be provided, if needed.

The following TEAE summaries will be generated:

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE
  - Grade ≥3 TEAE
  - Grade 3 or 4 TEAE
  - Grade 5 TEAE (any TEAE with a fatal outcome during the treatment period)
  - Serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent or premature treatment discontinuation.

13.9.4.3 Deaths

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (pretreatment, on-treatment, posttreatment)

A listing of deaths will be provided.

13.9.4.4 Clinical laboratory evaluations

For patients with multiple occurrences of the same laboratory variable during the on-treatment period, the maximum grade (worst) per patient will be used. Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. Each test result will be graded by NCI common terminology criteria (version 4.0.3). The number of patients with abnormal lab tests at baseline will be presented by grade. The frequency of patients in each grade of lab tests during treatment will be summarized (similar analysis will be performed based on data recorded at Cycle 1). When appropriate, the summary table will present the frequency of patients with any grade of abnormal laboratory tests and with Grade 3 or 4 of abnormal laboratory tests.

13.9.4.5 Vital signs

The summary statistics (including mean, median, standard error, minimum and maximum) of all vital signs variables (raw data and changes from baseline) will be calculated for each visit or study endpoint (baseline, each post baseline time point, last on treatment value and/or worst value) by dose level. Mean changes from baseline with the corresponding standard error (or boxplots) will be plotted over time (at same time points) in each dose level.

13.9.4.6 Analyses of other safety variables

Target engagement will be summarized by descriptive statistics and will be displayed with waterfall plots.

13.9.5 Analyses of pharmacokinetic and pharmacodynamic variables

13.9.5.1 Analyses of pharmacokinetic variables

Individual plasma concentrations and PK parameters of amcenestrant when given as monotherapy, and then of amcenestrant and palbociclib or amcenestrant and alpelisib or amcenestrant and everolimus or amcenestrant and abemaciclib when given in combination will be tabulated with standard descriptive statistics by dose level and study part under the responsibility of the PKDM department. Individual and mean profiles will be presented graphically.

The following statistical analyses will be performed for amcenestrant.

Dose proportionality will be assessed on data from Arm #1 Parts A of the QD regimen using a power model on C_{max}, and AUC_{0-24} on Day 1 and Day 22.

Accumulation ratio (Day 22 or Day 21/Day 1) for C_{max} and AUC_{0-24} (amcenestrant QD regimen) or AUC_{0-12} (amcenestrant BID regimen) for each dose level and dosing regimen will be estimated with 90% CIs using a linear fixed effects model on log transformed parameters (Arm #1, #2, #4, and #5 [Parts A, B, C, D, H, I, J, and K]).

Within-subject and total standard deviations for $\log(C_{max})$ and $\log(AUC_{0-24})$ will be estimated (Arm #1 and #2 [Parts A, B, C and D]).

The food effect will be assessed by comparing AUC_{0-24} and C_{max} between Day 1/Cycle 1 and Day 3/Cycle 1 Arm #1 Part A.

4β-hydroxycholesterol concentration ratio (Day 22/Day 1) will be estimated with 90% CI.

Time dependence will be investigated with plasma concentration observed before treatment administration (C_{trough}) after repeated administration, if relevant, using descriptive statistics and concentration versus day graphs over Cycle 1 and 2 (Arm #1 and #2 [Part A/B and C/D]).

Effect of palbociclib, alpelisib, everolimus or abemaciclib on amcenestrant

PK parameters of amcenestrant when given with palbociclib (Arm #2 Part C/D), alpelisib (Arm #3 Part F/G), everolimus (Arm #4 Part H/I) or abemaciclib (Arm #5 Part J/K) will be compared to PK parameters of SERD when given as single agent (Arm #1 Part A/B).

For amcenestrant BID regimen, similar analyses as for QD regimen will be performed on PK parameters, when applicable, except that AUC_{0-24} will have to be replaced by AUC_{0-12} when needed.

4β-hydroxy/total cholesterol concentration ratio (Cycle2/Cycle1) will be estimated with 90% CI.

For alpelisib parameters

Effect of amcenestrant treatment on alpelisib exposure (C_{max} and AUC_{0-24h}) will be assessed with a linear mixed effect model for each amcenestrant dose level. Treatment (amcenestrant with alpelisib/alpelisib alone) differences and 90% CIs will be computed by first taking the mean logarithmic differences within the mixed model framework, and then converting them to ratios of geometric means using the anti-logarithmic transformation.

13.9.5.2 Analyses of pharmacodynamic variables

Pharmacodynamic variables (such as ^{18}F-FES PET scan results) will be summarized by dose level using descriptive statistics and waterfall plots.

13.9.6 Analyses of antitumor activity/efficacy variables

The following variables may be calculated for the efficacy population:

- ORR according to RECIST v1.1
- Response duration defined as the time from initial response to the first documented tumor progression
- CBR (CR + PR + SD ≥24 weeks) per RECIST v.1.1
- Time to first tumor response (CR or PR) in Parts B, D and G defined as time from first amcenestrant intake to the first observation of PR or CR
- Progression-free survival (PFS)

The ORR and response duration will be described along with relevant parameters (characteristics of patients/disease). If appropriate, summaries will be provided.

13.10 INTERIM ANALYSIS

In Arm #1 Part B, an interim analysis is planned when 45 patients are treated in order to decide, based on preset criteria, if the recruitment of planned additional patients is justified. If 4 or less responses (CR + PR) are observed on the first 45 patients evaluable for response, the study will be stopped for futility.

In order to support project strategic planning and design of future studies, interim analyses may be conducted during the study in addition to the futility interim analyses described in Section 13.1. They will have no impact on the trial itself. Within the framework of these analyses, calculations of posterior probabilities for response rate will be performed.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff, and subinvestigator(s), in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for Good Clinical Practice (GCP), all applicable laws, rules, and regulations.

Information regarding the clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

14.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the study, including the written information giving approval/favorable opinion by the IRB/IEC. All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to the patient's participation in the clinical trial, the written Main ICF should be signed, and for Arm#3, the Pre-Screening ICF must be signed prior to the PIK3CA testing and signing of the Main ICF (ie, start of the screening procedures). Both ICFs must be signed with the patient's name, and must be dated by the patient or the patient's legally acceptable representative, as well as the person who conducted the informed consent discussion. In addition, in the Main ICF, patients will have an option to select the blood collection for optional pharmacogenetics testing (DMET). A copy of both signed and dated written ICFs will be provided to the patient.

Both, the Main and Pre-Screening ICFs which will be used by the Investigator for obtaining the patient's informed consent, must be reviewed and approved by the Sponsor prior to the submission to the appropriate IRB/IEC) for approval/favorable opinion.

14.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, ICF, Investigator's Brochure with any addenda, Investigator's curriculum vitae, etc) and the date of the review should be clearly stated on the written IRB/IEC approval/favorable opinion.

The study treatment will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report will be sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the eCRF, discrepancy resolution form [DRF], or other appropriate instrument) in an accurate manner according to the instructions provided and to ensure direct access to source documents by the Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All subinvestigators shall be appointed and listed in a timely manner. The subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

15.2 RESPONSIBILITIES OF SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the eCRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, study treatment allocation, patient compliance with the study treatment regimen, study treatment accountability, concomitant therapy use, and quality of data.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents, except for the preidentified source data directly recorded in the eCRF. The ICF will include a statement by which the patient allowing the Sponsor's duly authorized personnel, the IRB/IEC, and the regulatory authorities to have direct access to original medical records which support the data on the eCRF (eg, patient's medical file, appointment books, original laboratory

records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality rules).

15.4 USE AND COMPLETION OF CASE REPORT FORMS AND ADDITIONAL REQUESTS

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used) designed by the Sponsor to record (according to the Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All eCRFs should be completed in their entirety to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor when available in the eCRF may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

15.5 USE OF COMPUTERIZED SYSTEMS

Procedures shall be employed and controls designed to ensure the confidentiality of electronic records. Such procedures and controls shall include validation of systems to ensure accuracy and reliability, ability to generate accurate and complete copies of records, protection of records to enable retrieval, use of secure, computer-generated, time-stamped entries, use of operational system checks, use of device checks to determine validity of source data input, determination that person who develop, maintain, or use such systems have adequate education and training, the establishment and adherence of written policies to deter record falsification, the use of appropriate controls over systems documentation including the distribution of or use of documentation for system operation and maintenance, and revision and change control procedures which document time-sequenced development and modifications of systems documentation.

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

15.6 DATA QUALITY ASSURANCE

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.

16 ADDITIONAL REQUIREMENTS

16.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification, and training of each Investigator and subinvestigator will be signed, dated, and provided to the Sponsor prior to the beginning of the clinical trial.

16.2 RECORD RETENTION IN STUDY SITES(S)

The Investigator must maintain confidential all study documentation and take measures to prevent accidental or premature destruction of these documents.

It is recommended that the Investigator retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

16.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the eCRFs, the Investigator's Brochure, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the IRB/IEC is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the subinvestigators of the confidential nature of the clinical trial.

The Investigator and the subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

16.4 PROPERTY RIGHTS

All information, documents, and study treatment provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff/subinvestigator not to mention any information regarding the product in any application for a patent or for any other intellectual property rights.

All the results, data, documents, and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market, or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

16.5 DATA PROTECTION

- The patient's personal data, which may be included in the Sponsor database, shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding the Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject race/ethnicity will be collected in this study because these data are required by several regulatory authorities.

16.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy as required by applicable law.
An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

16.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified, and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

16.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

16.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the study treatment leads to doubt as to the benefit/risk ratio
- Patient enrollment is unsatisfactory
- The Investigator has received from the Sponsor all study treatment, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon
- Noncompliance by the Investigator or subinvestigator, or delegated staff with any provision of the clinical trial protocol, or breach of any applicable laws, regulations, or ICH GCP guidelines
- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

16.8.2 By the Investigator

The Investigator may terminate his/her participation upon 30 days prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

16.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a CSR and to provide a summary of study results to Investigator.

16.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold his approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within 12 months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or of its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

17 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the ICF. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised ICF prior to implementation of the change and patient signature should be recollected if necessary.

18 BIBLIOGRAPHIC REFERENCES

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19 APPENDICES

Appendix A Eastern cooperative oncology group performance status scale

Performance Status	Description
0	Normal, fully functional
1	Fatigue without significant decrease in daily activity
2	Fatigue with significant impairment of daily activities or bed rest <50% of waking hours
3	Bed rest/sitting >50% of waking hours
4	Bedridden or unable to care for self

Appendix B National cancer institute common terminology criteria for adverse events

Refer to NCI-CTCAE v.4.03 (2) in the Study Reference Manual, or online at the following NCI website: http://ctep.cancer.gov/reporting/ctc.html

Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.

When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.

The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.

An accurate baseline prior to therapy is essential.

Appendix C Modified response evaluation criteria in solid tumors (RECIST 1.1)

Details provided in bibliographic reference (40).

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or nonmeasurable as follows:

Measurable

- *Tumor lesions*: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable).
  - 20 mm by chest X-ray.
- *Malignant lymph nodes*: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed (see Special Issue 15 [40]). See also notes below on "Baseline documentation of target and nontarget lesions" for information on lymph node measurement.

Non-measurable

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Methods of measurement

- Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

- Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

- *Chest X-ray*: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- *CT, MRI*: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).
- *Ultrasound*: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

- *Endoscopy, laparoscopy*: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- *Tumor markers*: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- *Cytology, histology*: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor response evaluation

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either TTP or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having nonmeasurable disease only are also eligible.

Response Criteria

	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.s.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of nontarget lesions	
Complete Response (CR):	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
Incomplete Response/Stable Disease (SD):	Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below)[a] of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression).

a Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

It is assumed that at each protocol specified time point, a response assessment occurs. The following table provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered unevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as described above.

Appendix D Standard meal example

Food	Amount
Slices of bread	40 g
Jam	30 g
Butter	10 g
Semi skimmed milk	150 mL
or powdered milk	15 g
or natural yogurt	1

This type of diet generally contains approximately 9% protein, 27% lipids, and 64% carbohydrate, which provides about 400 to 500 kcal.

No fruit juice.

Appendix E List of CYP3A4 prohibited modulators

Concomitant administration of medications that are:

- Strong CYP3A4 inhibitors are not permitted in Arm #1 Part B (Cycle 1), Arm #2 Part C and D, Arm #4 (Parts H and I), and Arm #5 (Parts J and K)
- Moderate CYP3A4 inhibitors are not permitted in Arm #1 Part B (Cycle 1) and Arm #4 (Parts H and I)
- Strong CYP3A inducers are not permitted in any part of the study

The following tables were extracted in January 2017 from the Drug- Drug Interaction Database from the University of Washington (www.druginteractioninfo.org).

STRONG CYP3A INHIBITORS			
CYP3A inhibitors	**Precipitant Therapeutic Class**	**Victim (oral, unless otherwise specified)**	**AUC Ratio**
Potent CYP3A Inhibitors (yielding substrate AUCratio >5)			
Telaprevir	Antivirals	midazolam	13,5
Indinavir /RIT	Protease inhibitors	alfentanil	36,50
Tipranavir/RIT	Protease inhibitors	midazolam	26,91
Ritonavir	Protease inhibitors	midazolam	26,41
Cobicistat (GS-9350)	None	midazolam	19,03
Indinavir	Protease inhibitors	vardenafil	16,25
Ketoconazole	Antifungals	midazolam	15,90
Troleandomycin	Antibiotics	midazolam	14,80
Saquinavir / RIT	Protease inhibitors	midazolam	12,48
Itraconazole	Antifungals	midazolam	10,80
Voriconazole	Antifungals	midazolam	9,63
Mibefradil	Calcium Channel Blockers	midazolam	8,86
Clarithromycin	Antibiotics	midazolam	8,39
Danoprevir/RIT	Antivirals	midazolam	13,42
Lopinavir / RIT	Protease inhibitors	alfentanil	11,47
Elvitegravir / RIT	Treatments of AIDS	midazolam	12,80
Posaconazole	Antifungals	midazolam	6,23
Telithromycin	Antibiotics	midazolam	6,2
Grapefruit Juice DS	Food Products	midazolam	5,95
Conivaptan	Diuretics	midazolam	5,76
Nefazodone	Antidepressants	midazolam	5,44
Nelfinavir	Protease inhibitors	midazolam	5,29
Saquinavir	Protease inhibitors	midazolam	5,18
Boceprevir	Antivirals	midazolam	5,05
Idelalisib	Kinase inhibitors	midazolam	5,15
LCL161	Cancer treatments	midazolam	8,80
VIEKIRA PAK	Antivirals	tacrolimus	55,76

MODERATE CYP3A INHIBITORS			
CYP3A inhibitors	**Precipitant Therapeutic Class**	**Victim (oral, unless otherwise specified)**	**AUC Ratio**
Moderate CYP3A Inhibitors (AUCratio ≥2 and <5)			
Erythromycin	Antibiotics	midazolam	4,99
Fluconazole	Antifungals	midazolam	4,93
Atazanavir / RIT	Protease inhibitors	maraviroc	4,90
Darunavir	Protease inhibitors	saquinavir	4,90
Diltiazem	Calcium Channel Blockers	midazolam	4,06
Darunavir / RIT	Protease inhibitors	sildenafil	4,00
Dronedarone	Antiarrhythmics	simvastatin	3,66
Crizotinib	Kinase Inhibitors	midazolam	3,65
atazanavir	Protease Inhibitors	maraviroc	3,57
GSK2647544	Alzheimer's Disease & Dementia	simvastatin	3,30
aprepitant	Antiemetics	midazolam	3,29
casopitant	Antiemetics	midazolam	3,13
amprenavir	Protease Inhibitors	rifabutin	2,93
faldaprevir	Antivirals	midazolam	2,92
imatinib	Antineoplastic Agents	simvastatin	2,92
verapamil	Calcium Channel Blockers	midazolam	2,92
netupitant	Antiemetics	midazolam	2,44
nilotinib	Kinase Inhibitors	midazolam	2,40
grapefruit juice	Food Products	midazolam	2,39
tofisopam	Benzodiazepines	midazolam	2,36
cyclosporine	Immunosuppressants	midazolam	2,21
ACT-178882	Renin Inhibitors	midazolam	2,19
ciprofloxacin	Antibiotics	sildenafil	2,12
schisandra sphenanthera	Herbal Medications	midazolam	2,05
isavuconazole	Antifungals	midazolam	2,03
cimetidine	H-2 Receptor Antagonists	midazolam	2,02
FK1706	Central Nervous System Agents	midazolam	2,01

The following tables were extracted in April 2019 from the Drug-Drug Interaction Database from the University of Washington (www.druginteractioninfo.org).

STRONG CYP3A INDUCERS					
Inducers	**Therapeutic Class**	**Victim (oral unless otherwise specified)**	**% of AUC decrease**	**% oral CL increase**	**Precipitant dose (oral)**
Potent Inducers of CYP3A (AUC decreased by ≥80% or CL increased by more than 5-fold [400%])					
Rifampin	Antibiotics	Budesoinide	99.7	36904.5	600 mg QD (7 days)
Mitotane	Other Antineoplastics	Midazolam	94.5	Not provided	Maximum of 3.5g TID (chronic therapy)
Avasimibe	Other Antilipemics	Midazolam	93.5	Not provided	750 mg/day (7 days)
Phenytoin	Anticonvulsants	Nisoldipine	89.5	Not provided	200-450 mg/day (chronic treatment)
Carbamazepine	Anticonvulsants	Quetiapine	86.6	643.1	200 mg TID (26 days)
Enzalutamide	Antiandrogens	Midazolam	85.9	Not provided	160 mg QD (85±3 days)
St John's Wort extract	Herbal Medicines	Midazolam	80.0	Not provided	300 mg TID 14 days
Rifabutin	Antibiotics	Delavirdine	Not provided	458.0	300 mg QD 14 days
Phenobarbital	Anticonvulsants	Verapamil	76.6	400.9	100 mg QD 21 days

MODERATE CYP3A INDUCERS					
Inducers	**Therapeutic Class**	**Victim (oral unless otherwise specified)**	**% of AUC decrease**	**% oral CL increase**	**Precipitant dose (oral)**
Moderate inducers of CYP3A (AUC decreased by 50-80% or CL increased by 2 to 5-fold [100%-400%])					
Ritonavir and St John's Wort	None	Midazolam	77.2	Not provided	Ritanovir 300 mg BID; St John's Wort 300 mg TID (14 days)
Semagacestat	Alzheimer's Treatments	Midazolam	76.4	324.6	140 mg QD (10 days)
Tipranavir and ritonovir	Protease inhibitors	Saquinavir	75.6	Not provided	Tipranavir 500 mg; ritonavir 200 mg BID (14 days)
Bosentan	Endothelin receptor antagonist	Sildenafil	69	239.8	62.5-125 mg BID 8 weeks
Genistein	Food Products	Midazolam	13.7	136.9	1000 mg QD (14 days)
hioridazine	Antipsychotics	Quetiapine	68.7	104.5	100-300 mg QD (15 days)
Naficillin	Antibiotics	Nifedipine	62.6	145.1	500 mg 4 times daily 5 days
Talviraline	NNRTIs	Indinavir	61.7	181.2	500 mg TID 14 days
Efavirenz	NNRTIs	Simvastatin acid	60.4	Not provided	600 mg QD 28 days
Lopinavir	Protease inhibitors	Amprenavir	59.7	Not provided	400 mg BID (4 weeks)
Modafinil	Psycho-stimulants	Triazolam	57.6	35.7	200-400 mg QD 28 days
Etravirine	NNRTIs	Sildenafil	56.7	Not provided	800 mg BID 13.5 days
Lersivirine	NNRTIs	Midazolam	51.4	105.5	1000 mg BID (14 days)

Appendix F List of CYP substrate with a narrow therapeutic range and list of substrates mainly metabolized by CYP3A/2B/2C/UGT

Patients treated or intended to be treated with the following drugs presented as CYP substrates with narrow therapeutic range should be carefully monitored:

In vivo CYP3A Narrow Therapeutic Range (NTR) Substrates

CYP enzyme	NTR Substrates
CYP3A	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, quinidine, sirolimus, tacrolimus, cisapride, astemizole, terfenadine, pimozide

CYP Substrates with a Narrow Therapeutic Range - drugs with an exposure-response relationship that indicates that relatively small increases in their exposure levels by coadministered CYP inhibitors may lead to safety concerns

Patients treated or intended to be treated with the following drugs metabolized by CYP3A/CYP2B6/CYP2C and/or UGT should be carefully monitored for their efficacy, since their exposure may be decreased by amcenestrant:

Drugs mainly metabolized by CYP3A, CYP2Cs and/or UGTs:

Drug	Therapeutic Class
(R)-(-)-hexobarbital	Hypnotics - Sedatives
(R)-mephobarbital	Anticonvulsants
(S)-mephenytoin	Anticonvulsants
(S)-warfarin	Anticoagulants and Antiplatelets
alfentanil	Opioids
alisporivir	Antivirals
almorexant	Hypnotics - Sedatives
alpha-dihydroergocryptine	Dopaminergic Agonists
aplaviroc	CCR5 Receptor Antagonists
aprepitant	Neurokinin-1 Receptor Antagonists
asunaprevir	Antivirals
atazanavir	Protease Inhibitors
atorvastatin	HMG CoA Reductase Inhibitors (Statins)
avanafil	Erectile Dysfunction Treatments
benzbromarone	Anticoagulants and Antiplatelets
blonanserin	Antipsychotics
brecanavir	Protease Inhibitors
brotizolam	Benzodiazepines
budesonide	Corticosteroids
bupropion	Anticoagulants and Antiplatelets
buspirone	Anxiolytics
capravirine	Antivirals
casopitant	Neurokinin-1 Receptor Antagonists
celecoxib	NSAIDS

Drug	Therapeutic Class
clobazam (parent drug)	Benzodiazepines
conivaptan	Vasopressin Antagonists
danoprevir	Antivirals
daprodustat	Other
darifenacin	Muscarinic Antagonists
darunavir	Protease Inhibitors
dasabuvir	Antivirals
diazepam	Benzodiazepines
dronedarone	Antiarrhythmics
ebastine	H1 Receptor Antagonists
efavirenz	Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
eletriptan	Triptans
eliglustat (in subjects CYP2D6 PMs)	Glucosylceramide Synthase Inhibitors
elvitegravir	HIV-Integrase Strand Transfer Inhibitors
eplerenone	Diuretics
everolimus	Immunosuppressants
felodipine	Calcium Channel Blockers
gliclazide	Sulfonylureas
glimepiride	Sulfonylureas
glipizide	Sulfonylureas
ibuprofen	NSAIDS
indinavir	Protease Inhibitors
isavuconazole	Antifungals
itacitinib	Kinase Inhibitors
ivabradine	Cardiovascular Drugs
ivacaftor	Miscellaneous Agents
lansoprazole (dexlansoprazol)	Proton Pump Inhibitors
levomethadyl (LAAM)	Drug Addiction Treatments
lomitapide	Other Antilipemics
lopinavir	Protease Inhibitors
lornoxicam	NSAIDS
lovastatin	HMG CoA Reductase Inhibitors (Statins)
lumefantrine	Antimalarials
lurasidone	Antipsychotics
maraviroc	CCR5 Receptor Antagonists
meloxicam	NSAIDS
midazolam	Benzodiazepines
morphothiadin	Antivirals
naloxegol	Gastrointestinal Agents
nisoldipine	Calcium Channel Blockers
omeprazole	Proton Pump Inhibitors
pantoprazole	Proton Pump Inhibitors
paritaprevir	Antivirals

Drug	Therapeutic Class
perospirone	Antipsychotics
piroxicam	NSAIDS
proguanil (prodrug)	Antimalarials
quetiapine	Antipsychotics
rabeprazole	Proton Pump Inhibitors
repaglinide	Meglitinides
saquinavir	Protease Inhibitors
sildenafil	Erectile Dysfunction Treatments
simeprevir	Protease Inhibitors
simvastatin	HMG CoA Reductase Inhibitors (Statins)
sirolimus	Immunosuppressants
tacrolimus	Immunosuppressants
terfenadine	H1 Receptor Antagonists
ticagrelor	Anticoagulants and Antiplatelets
tilidine	Treatments of Pain and Inflammation
tilidine	Treatments of Pain and Inflammation
tipranavir	Protease Inhibitors
tolbutamide	Sulfonylureas
tolvaptan	Vasopressin Antagonists
triazolam	Benzodiazepines
ubrogepant	Migraine Treatments
ulipristal	Hormones
(R)-(-)-hexobarbital	Hypnotics - Sedatives
(R)-mephobarbital	Anticonvulsants
clobazam (parent drug)	Benzodiazepines
diazepam	Benzodiazepines
gliclazide	Sulfonylureas
pantoprazole	Proton Pump Inhibitors
proguanil (prodrug)	Antimalarials
rabeprazole	Proton Pump Inhibitors

Appendix G List of BCRP inhibitors, CYP2C9 substrates and P-gp, BCRP and OAT3 substrates

The following tables were extracted from the FDA website (41).

BCRP inhibitors

Transporter	Gene	Inhibitor
BCRP	ABCG2	curcumin, cyclosporine A, eltrombopag

Note: Criteria for selecting BCRP in vivo inhibitor are as follows:

- AUC fold-increase of sulfasalazine ≥1.5 with co-administration and (2) in vitro inhibitor. Cyclosporine A and eltrombopag were also included, although the available DDI information was with rosuvastatin, where inhibition of both BCRP and OATPs may have contributed to the observed interaction.

This table is prepared to provide examples of clinical inhibitors for various transporters and not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database (42).

CYP2C9 substrates

	Sensitive substrates	Moderate senstive substrates
CYP2C9	celecoxib[a]	glimepiride, phenytoin, tolbutamide, warfarin

a Listed based on pharmacogenetic studies

Note: Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.

This table is prepared to provide examples of clinical substrates and not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database (42).

P-gp, BCRP and OAT3 substrates

Transporter	Gene	Substrate
P-gp	ABCB1	dabigatran etexilate, digoxin, fexofenadine[a]
BCRP	ABCG2	rosuvastatin, sulfasalazine
OAT1 OAT3	SLC22A6, SLC22A8	adefovir[b], cefaclor, ceftizoxime, famotidine[c], furosemide, ganciclovir[b], methotrexate, oseltamivir carboxylate[c], penicillin G[c]

a Fexofenadine is a substrate for both P-gp and OATP1B.
b In vitro data suggested higher contribution of OAT1 than OAT3.
c In vitro data suggested higher contribution of OAT3 than OAT1.

Note: Criteria for selecting clinical substrates are as follows:

- P-gp: (1) AUC fold-increase ≥2 with verapamil or quinidine co-administration and (2) in vitro transport by P-gp expression systems, but not extensively metabolized.
- BCRP: (1) AUC fold-increase ≥2 with pharmacogenetic alteration of ABCG2 (421C>A) and (2) in vitro transport by BCRP expression systems.
- OAT1/OAT3: (1) AUC fold-increase ≥1.5 with probenecid co-administration, (2) fraction excreted unchanged into urine as an unchanged drug ≥0.5, and (3) in vitro transport by OAT1 or OAT3 expression systems.

This table is prepared to provide examples of clinical substrates for various transporters and not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database (42).

Appendix H In vivo Inhibitors of P-gp Probes

Inhibitor[a]	Therapeutic Class	Inhibitor Dose (oral)	Substrate[b]	Max AUCR or CL Ratio
alogliptin	Dipeptidyl Peptidase-4 Inhibitors	100 mg QD (7 days)	fexofenadine	1.26
amiodarone	Antiarrhythmics	600 mg SD	dabigatran[c]	1.58
		400 mg/day (5 days)	digoxin (IV)	0.74 (CL ratio)
		800 mg/day (7 days)	digoxin	1.68
asian ginseng (Panax ginseng)	Herbal Medications	70 mL fermented red ginseng liquid (14 days)	fexofenadine	1.31
asunaprevir	Antivirals	200 mg BID (13 days)	digoxin	1.30
asunaprevir/ beclabuvir/daclatasvir	Antivirals	200 mg/75 mg/30 mg BID (15 days)	digoxin	1.22
atorvastatin (acid)	HMG CoA Reductase Inhibitors (Statins)	80 mg QD (10 days)	digoxin	1.20 (C_{max} ratio)
AZD5672	CCR5 Receptor Antagonists	150 mg QD (13 days)	digoxin	1.33
azithromycin	Antibiotics	250 mg QD (5 days)	fexofenadine	1.72
canagliflozin	Sodium-dependent Glucose Cotransporter 2 (SLGT2) Inhibitors	300 mg QD (7 days)	digoxin	1.20
capmatinib	Kinase Inhibitors	400 mg BD (median: 7.14 weeks)	digoxin	1.47
captopril	Angiotensin Converting Enzyme (ACE) Inhibitors	12.5 mg TID (7 days)	digoxin	1.39
carvedilol	Alpha/Beta Adrenergic Antagonists	6.25 mg BID (7 days)	digoxin	1.57
cimetidine	H-2 Receptor Antagonists	400 mg SD	digoxin	1.26
clarithromycin	Antibiotics	500 mg BID (5 days)	dabigatran[d]	4.02
		500 mg BID (7 days)	digoxin	1.68
		500 mg BID (7 days)	fexofenadine	2.54
clopidogrel	Anticoagulants and Antiplatelets	300 mg SD	dabigatran	1.35
cobicstat	Pharmacokinetic Enhancer	150 mg QD (22 days)	dabigatran	2.37
		150 mg QD (10 days)	digoxin	1.41 (C_{max} ratio)
conivaptan	Vasopressin Antagonist	40 mg BID (10 days)	digoxin	1.43
cremophor EL	Excipients	1440 mg SD	fexofenadine	1.28
cremophor RH	Excipients	600 mg TID (9 days)	digoxin	1.21
curcumin	Food Products	1000 mg QD (14 days)	talinolol	1.54
daclatasvir	Antivirals	60 mg QD (10 days)	digoxin	1.27
diltiazem	Calcium Channel Blockers	60 mg TID (10 days)	digoxin	1.44
diosmin	Herbal Medications	150 mg QD (10 days)	fexofenadine	1.66
diprafenone	Antiarrhythmics	100 mg TID (7 days)	digoxin	1.41 (C_{max} ratio)
dronedarone	Antiarrhythmics	400 mg BID (10 days)	digoxin	2.33
elagolix	Other	200 mg SD	digoxin	1.32
eliglustat	Glucosylceramide Synthase Inhibitors	100 mg (PMs) and 150 mg (others) (7 days)	digoxin	1.49

Inhibitor[a]	Therapeutic Class	Inhibitor Dose (oral)	Substrate[b]	Max AUCR or CL Ratio
erythromycin	Antibiotics	500 mg TID (7days)	fexofenadine	2.09
		2 g SD	talinolol	1.52
felodipine	Calcium Channel Blockers	2.5 mg SD	digoxin	1.49
flibanserin	Central Nervous System Agents	100 mg QD (8 days)	digoxin	1.93
fluvoxamine	Selective Serotonin Reuptake Inhibitors (SSRIs)	50 mg QD (7 days)	fexofenadine	1.78
fostamatinib	Other	0.25 mg QD (15 days)	digoxin	1.37
ginkgo (Ginkgo biloba)	Herbal Medications	120 mg TID (14 days)	talinolol	1.25
glecaprevir/ pibrentasvir	Antivirals	300 mg/120 mg QD (10 days)	dabigatran	2.38
		400 mg/120 mg QD (12 days)	digoxin	1.48
indinavir	Protease Inhibitors	80 mg TID (21 days)	fexofenadine	3.31
indinavir/ritonavir	Protease Inhibitors	800 mg/100 mg BID (1 day)	fexofenadine	4.84
isavuconazole	Antifungals	Not Provided	digoxin (not provided)	1.25
istradefylline	Other Antiparkinsonians	40 mg QD (21 days)	digoxin	1.21
itraconazole	Antifungals	200 mg QD (5 days)	dabigatran[d]	6.92
		200 mg QD (5 days)	digoxin	1.68
		100 mg BID (5 days)	fexofenadine	3.01
ivacaftor	Other	150 mg Q12H (9 days)	digoxin	1.32
ketoconazole	Antifungals	400 mg QD (8 days)	dabigatran	2.53
		400 mg QD (7 days)	fexofenadine	2.74
lapatinib	Kinase Inhibitors	Not Provided	digoxin	2.80
lopinavir/ritonavir	Protease Inhibitors	400 mg/100 mg BID (14 days)	digoxin	1.81
		400 mg/100 mg SD	fexofenadine	4.14
maribavir	Antivirals	400 mg BID (8 days)	digoxin	1.22
mibefradil	Calcium Channel Blockers	150 mg QD (7 days)	digoxin	1.31
mifepristone	Antiprogestins	1200 mg QD (10 days)	digoxin	1.36
milk thistle (Silybum marianum)	Herbal Medications	140 mg TID (14 days)	talinolol	1.30
mirabegron	Beta3-Adrenoreceptor Agonist	100 mg QD (14 days)	digoxin	1.26
nefazodone	Serotonin Modulators	200 mg BID (8 days)	digoxin	1.29 (C_{max} ratio)
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)	digoxin	1.35
neratinib	Kinase Inhibitors	240 mg QD (multiple doses)	digoxin	1.32
nifedipine	Calcium Channel Blockers	10 mg TID (7 days)	digoxin	1.23
nitrendipine	Calcium Channel Blockers	20 mg QD (7 days)	digoxin	1.16
ombitasvir/ paritaprevir/ ritonavir	Antivirals	150/100/25 mg QD (19 days)	digoxin	1.35
osimertinib	Kinase Inhibitors	80 mg SD	fexofenadine	1.54
paroxetine	Selective Serotonin Reuptake Inhibitors (SSRIs)	20 mg QD (7 days)	fexofenadine	1.38
pexidartinib	Kinase Inhibitors	1800 mg SD	digoxin	1.32 (C_{max} ratio)

Inhibitor[a]	Therapeutic Class	Inhibitor Dose (oral)	Substrate[b]	Max AUCR or CL Ratio
piperine	Food Products	20 mg QD (10 days)	fexofenadine	1.70
propafenone	Antiarrhythmics	300 mg TID (3 days)	digoxin (IV)	1.29
		600 mg QD (7 days)	digoxin	0.69 (CL ratio)
		250-500 mg/kg QD (7 days)	digoxin	0.33 (CL ratio)[e]
quercetin	Herbal Medications	500 mg TID (7 days)	fexofenadine	1.56
quinidine	Antiarrhythmics	1000 mg (200 mg Q2H)	dabigatran	1.53
		200 mg QID (6 days)	digoxin (IV)	0.36 (CL ratio)
		600 mg BID (8 days)	digoxin	2.66
		25 mg SD	fexofenadine	2.14
quinine	Antimalarial	200 mg TID (9 days)	digoxin (IV)	0.75 (CL ratio)
ranolazine	Cardiovascular Drugs	750 mg BID (6 days)	digoxin	1.88
rifampin	Antibiotics	600 mg QD SD	dabigatran[d]	2.32
		600 mg QD (28 days)	digoxin	1.46
		600 mg QD SD	fexofenadine	(S) 3.57 (R) 3.21[f]
ritonavir	Protease Inhibitors	100 mg QD (10 days; PBPK Modeling)	dabigatran	1.27
		300 mg BID (11 days)	digoxin (IV)	1.86
		400 mg BID (14 days)	digoxin	1.47
		200 mg TID (1 day), 300 mg BID (7 days), 400 mg BID (13 days)	fexofenadine	2.75
rolapitant	Antiemetics	180 mg SD	digoxin	1.27
rucaparib	Cancer Treatments	600 mg TID (12 days)	digoxin	1.21
saquinavir/ ritonavir	Protease Inhibitors	1000 mg/100 mg BID (16 days)	digoxin	1.68
sarecycline	Antibiotics	150 mg SD	digoxin	1.26 (C_{max} ratio)
schisandra chinensis	Herbal Medications	300 mg BID (14 days)	talinolol	1.52
simeprevir	Antivirals	150 mg QD (7 days)	digoxin	1.39
sofosbuvir/ velpatasvir/ voxilaprevir	Antivirals	400/100/200 mg QD (11 days)	dabigatran	2.59
St. John's wort (Hypericum perforatum)	Herbal Medications	900 mg SD	fexofenadine	1.31
suvorexant	Hypnotics - Sedatives	40 mg (11 days)	digoxin	1.27
talinolol	Alpha/Beta Adrenergic Antagonists	100 mg SD	digoxin	1.23
telaprevir	Antivirals	750 mg TID (16 days)	digoxin	1.82
telithromycin	Antibiotics	800 mg QD (5 days)	digoxin	1.36
telmisartan	Angiotensin II Inhibitors (Angiotensin Receptor Blockers or ARBs)	120 mg QD (7 days)	digoxin	1.22
tezacaftor/ivacaftor	Other	100/150 mg QD (14 days)	digoxin	1.30
ticagrelor	Anticoagulants and Antiplatelets	400 mg QD (16 days)	digoxin	1.28
tipranavir/ritonavir	Protease Inhibitors	500/200 mg BID (2 days)	digoxin (IV)	1.46
		500/200 mg BID (2 days)	digoxin	1.65

Inhibitor[a]	Therapeutic Class	Inhibitor Dose (oral)	Substrate[b]	Max AUCR or CL Ratio
tocophersolan (TPGS, Vitamin E-TPGS)	Excipients	0.04% intraduodenal SD	talinolol	1.20
tolvaptan	Vasopressin Antagonists	60 mg QD (5 days)	digoxin	1.18
tucatinib	Kinase Inhibitors	300 mg BID (14 days)	digoxin	1.50
valbenazine	Central Nervous System Agents	80 mg SD	digoxin	1.33
valspodar (PSC 833)	Transporter Modulators	200 mg BID (5 days)	digoxin	3.05
vandetanib	Kinase Inhibitors	300 mg SD	digoxin	1.22
velpatasvir	Antivirals	100 mg QD (4 days)	digoxin	1.34
vemurafenib	Kinase Inhibitors	960 mg BID (28 days)	digoxin	1.91
venetoclax	Cancer Treatments	100 SD	digoxin	1.38 (C_{max} ratio)
verapamil	Calcium Channel Blockers	120 mg SD	dabigatran	2.42
		80 mg BID (4 days) then TID (10 days)	digoxin (IV)	1.24
		80 mg BID (4 days) then TID (10 days)	digoxin	1.50
		80 mg TID (6 days)	fexofenadine	2.51
vilazodone	Serotonin Modulators	Not Provided	digoxin	1.20
voclosporin	Immunosuppressants	0.4 mg/kg Q12H (11 days)	digoxin	1.25
vorapaxar	Anticoagulants and Antiplatelets	2.5 and 40 mg (7 days)	digoxin	1.57 (C_{max} ratio)
zanubrutinib	Kinase Inhibitors	160 mg BID (7 days)	digoxin	1.34 (C_{max} ratio)

a Inhibitors are presented alphabetically due to differences in the sensitivity of substrates
b Oral administration, unless otherwise indicated
c Administered as the prodrug, dabigatran etexilate, which is a P-gp substrate, though the active dabigatran, for which the PK is measured, is not
d Micro dose study
e Study was performed in a pediatric population
f AUC ratios for repeated dosing of rifampin (6 days): (S) - 2.40, (R) - 1.90 (Accession #23115085)
* Probes were selected based on regulatory agency recommendations: dabigatran etexilate, digoxin, fexofenadine (FDA, EMA, MHLW), and talinolol (FDA)
Note - fexofenadine and talinolol are also transported by other transporters, such as OATPs

Appendix I Abbreviated modification of diet in renal disease formula

GFR (mL/min/1.73 m^2) = 175 x (Scr) -1.154 x (Age)-0.203 x (0.742 if Female) x (1.212 if African-American).

Appendix J Contingency measures for a regional or national emergency that is declared by a governmental agency

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, and terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency. The decision for each individual participant to remain and/or start in the study should be made on a case by case basis based on best Investigator medical judgment. The clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment and the evolving situation at the site (Section 11.3). However, in case new participant eligible for the trial, the PI/site should assess the capacity to maintain these patients into the trial before any screening procedures will start. If the site cannot guarantee an accurate follow-up in the context of the trial, alternative treatment outside the clinical trial should be proposed.

When participants are already randomized and/or treated, attempts should be made to perform all assessments in accordance with the protocol to the extent possible.

When possible, the focus should be on Investigational Medicinal Product (IMP) administration and safety blood collection (eg, biochemistry and hematology). However, all efforts should be made to perform the measurements of key parameters for efficacy endpoints (eg, tumor assessments). The deviations from the study protocol (eg, treatment delay, omission, tests not performed…) should be documented in the source document and collected in the appropriate pages of the eCRF.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc.) may be planned for the collection of possible safety and/or efficacy data (eg safety assessments, efficacy assessments especially the tumor assessment, PRO).
- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed.
- The Direct-to-Patient (DTP) supply of the IMP from the site/sponsor where allowed by local regulations and agreed upon by participant. (Section 8.1).

Contingencies implemented due to emergency will be documented.

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs) (Section 14.1).

Appendix K Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Clinical Trial Summary.

AMENDED PROTOCOL 09 (Date 23 March 21)

This Amended Protocol 09 (Amendment 09) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The objective of the amendment is to:

1. Discontinue Arm #1 study Part A-BID dose levels which enrolled 6 patients. Considering that PK, PD, safety and activity data so far in AMEERA-1 and AMEERA-2 studies as well as healthy volunteers' study provided sufficient information regarding the BID dosing, additional exploration of this dosing in monotherapy (Arm #1 Part A-BID and Part B-BID) is not to be considered as needed anymore. Therefore, Arm #1 Part A-BID and Part B-BID will be removed from the study.
2. Addition of 2 new Arms to investigate safety, efficacy, pharmacokinetic and pharmacodynamic of 2 new combination therapies: a) combination of amcenestrant with everolimus (Arm #4), and b) combination of amcenestrant with abemaciclib (Arm #5). In both cohort, amcenestrant will be administered at the RP2D established in combination so far, ie, 200 mg/day and both everolimus and abemaciclib will be administered at 2 different approved doses in a dose escalation part (Arm #4 Part H and Arm#5 Part J, respectively), followed by an expansion part at the selected dose (Arm #4 Part I and Arm #5 Part K respectively).

   In this study, each, everolimus and abemaciclib will be used at their approved, standard dose levels of 5 mg and 10 mg QD (everolimus) / 100 mg and 150 mg BID (abemaciclib) by oral route (with, as per label for both drugs, permitted dose reductions, if needed) in combination with amcenestrant 200 mg QD dose which was selected dose for the combination therapy. Additionally, in each of the combinations, a possibility of exploring additional doses of amcenestrant (eg, 300 mg QD or 400 mg QD etc.) with everolimus / abemaciclib could be considered depending on safety and pharmacokinetics profile of both combinations.
3. Change of the compound name, SAR439859 to the INN name: amcenestrant.
4. Additional tablet strength of alpelisib (ie, 150 mg) is added to the existing tablet strengths of 50 mg and 200 mg to secure the IMP for both study parts in Arm #3
5. Additional safety language for Arm#3 with more detailed instructions for DLTs and alpelisib dose modification

6. Additional exclusion criteria (E38) to prevent potential DDI with everolimus in Arm #4. The treatments listed in E38, were also prohibited as concomitant treatment in Arm #4.
7. Correct typo and inconsistencies

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Global	Updated SAR439859 to amcenestrant throughout document.	This content was updated to provide the INN name of the product.
Global	Corresponding treatment arms to study parts were added throughout the document. Arm #1 is Part A/B, Arm #2 is Part C/D, Arm #3 is F/G, Arm #4 is H/I, and Arm #5 is J/K..	These study arms were included in order to provide more organization and clarity throughout the document.
Global	New combination study arms added throughout the document.	This content was added in order to provide new study parts for the AMEERA-1 study design.
Clinical Trial Summary	Overall number of sites updated to 40 sites	This content was updated in order to reflect the new expected number of sites
Clinical Trial Summary and Section 4.4.4.1 Part H (Dose escalation with everolimus), Section 4.4.4.2 Part I (Dose expansion, combination with everolimus), Section 4.4.5.1 Part J (Dose escalation phase with abemaciclib), Section 4.4.5.2 Part K (Dose expansion, combination with abemaciclib)	New combination study arms, ie Arm #4 (Part H and I) and Arm#5 (Part J and K) were added as new sections.	This content was added in order to reflect the new study design.
Clinical Trial Summary, Section 5.1 Primary objections, Section 5.2 Secondary objectives, Section 5.3 exploratory objectives, Section 9.1.1 Dose limiting toxicities	Primary, secondary, and exploratory objections and endpoints were modified to include the new study arms and Arm #3 (Part F).	This content was modified to reflect the new study design and to eliminate redundancies.
Clinical Trial Summary and Section 6.2.1 Starting Dose and Dose Levels, and Section 8.1.2.1 Amcenestrant	Deleted “An additional BID dose could be tested in Part C assuming that BID monotherapy in Part A indicates a benefit compared to the RD given QD”.	This content was removed due to study design changes.
Clinical Trial Summary and Section 6.2.1 Starting dose and dose levels	Footnote b in Table 3 amcenestrant and alpelisib in Part F was updated.	Footnote b was updated to provide clarity regarding the dose levels tested.
Clinical Trial Summary, Section 6.5.3 Arm #4 Dose Modification in Parts H and I, Section 6.5.4 Arm #5 Dose modification in Parts J and K	Dose modification for Arm #4 (Part H and I) and Arm#5 (Part J and K) were added.	This content was added in order to reflect the new study design.
Clinical Trial Summary and Section 6.8.1 Duration of study participations for each patient	Content on COD and enrollment period was updated.	This content was updated in order to clarify when COD will occur and what is the expected enrollment period.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary and Section 7.2 Inclusion Criteria	I01, I05, and I06 were updated to include inclusion criteria for the new study arms. I10 clarified to specify two FDG PET/CT were done in Arm #1 Part A BID only.	This content was updated in order reflect the new study design and to provide clarity to the study design.
Clinicial Trial Summary and Section 7.3.2 Exclusion criteria related to the disease	E13, E25, E30, E31, E32, and E33 were updated to include exclusion criteria related to the new study parts New exclusion criteria E35, E36, E37, E38, and E39 were added.	This content was updated to reflect new study design and to provide clarity.
Clinical Trial Summary, Section 7.3.2 Exclusion criteria related to the disease, and Appendix E List of CYP3A4 prohibited modulators	Moderate CYP3A and CYP2C8 inducers were removed in E21 and Appendix E.	This content was updated to reflect new clinical results showing that a strong inducer (Rifampin) can lead to a modest decrease of amcenestrant exposure.
Clinical Trial Summary, Section 8.1.1.3 Alpelisib and Section 8.1.2.3 Alpelisib	Additional tablet strength of alpelisib (ie, 150 mg) is added as a possibility to the existing tablet strengths of 50 mg and 200 mg. Statement “2 x 50 mg tablets + 1 x 200 mg tablet” was removed.	This change reflects an update in the clinical supply due to uncertainities in supply caused by COVID-19.
Clinical Trial Summary, Section 8.1.1.4 Everolimus, Section 8.1.1.5 Abemaciclib, Section 8.1.2.4 Everolimus, Section 8.1.2.5 Abemaciclib, and Section 13.9.2 Extent of investigational medicinal product exposure	Content added regarding everolimus and abemaciclib as IMPs and how they can be taken.	This content was added to reflect the change in study design.
Clinical Trial Summary and Section 8.1.2.1 Amcenestrant	New content added on how amcenestrant will be taken for Arm #4 (Parts H and I) and Arm #5 (J and K).	This content was added to reflect new study design.
Clinical Trial Summary and Section 13.1 Determination of sample size	Sample size was changed to 251 patients.	This content was updated in order to reflect the addition of 2 new study Arms and removal of parts that are no longer occuring.
Clinical Trial Summary, Section 13.2.2 Sample size of the expansion phase for amcenestrant as monotherapy (Part B) and Section 13.10 Interim analysis	BID regimen and related information was removed for Part B.	This content was removed to reflect an update in the study design.
Clinical Trial Summary, Section 13.1 Determination of sample size, Section 13.5.1 Sample size of the dose escalation part for amcenestrant in combination with everolimus (Part H), Section 13.5.2 Sample size of the expansion phase for amcenestrant in combination with everolimus (Part I), Section 13.6.1 Sample size of the dose escalation part for amcenestrant in combination with abemaciclib (Part J), and Section 13.6.2 Sample size of the expansion phase for amcenestrant in combination with abemaciclib (Part K)	Sample size was adjusted and Arm #4 (Part H and I) and Arm#5 (Part J and K) sample size content were added.	This content was adjusted and added in order to reflect the sample size for new study parts.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary and Section 13.9.6 Analyses of antitumor activity/efficacy variables	Modified efficacy endpoint 'non-PFS rate at 6 months' to Progression Free Survival.	The PFS rate at 6 months was removed and replaced by PFS to better characterize the whole PFS curve.
Section 1.3 Study flowchart	Hematological and blood chemistry test frequency have been decreased after cycle 6 from every 2 weeks to every 4 weeks. Footnote b, d, e, f, g, h i, l, o, z, and aa were modified. Footnote gg, hh, and ii were added. Subsequent footnotes were realphabetized.	Footnotes were modified to provide clarity and inclusion of new footnote content for Arm #4 (Part H and I) and Arm#5 (Part J and K).
Section 1.4.1 Arm #1, Section 1.4.2 Arm #2, Section 1.4.3 Arm #3, Section 1.4.4 Arm #4, Section 1.4.4.1 Parts H and I, Section 1.4.5 Arm #5, 1.4.5.1 Parts J and K, Section 1.4.5.1.1 Parts J and K full PK sampling, Section 1.4.5.1.2 Part K, sparse PK sampling, Section 4.4.1 Arm #1, Section 4.4.2 Arm #2, Section 4.4.3 Arm #3, Section 4.4.4 Arm #4, Section 4.4.5 Arm #5, Section 13.2 Arm #1, Section 13.3 Arm #2, Section 13.4 Arm #3, Section 13.5 Arm #4, and Section 13.6 Arm #5	A new section for each study arm corresponding to a study part was created. Subsequent sections were reordered.	These sections were created in order to provide more organization and clarity throughout the document.
Section 1.4.1.1 Part A	Footnote d modified to only include FDG for Part A BID patients only.	The footnote was modified for clarification.
Section 4.1 Introduction	New content added on BOLERO-2 study. Reference was updated accordingly.	This content and reference was added in order to provide more context to the study.
Section 4.4 Rationale for the study and Section 9.1 Safety	Everolimus and abemaciclib were added as part of the section.	Everolimus and abemaciclib was added in order to reflect the new study design.
Section 4.4.3.1 Part F (Safety run-in phase with alpelisib)	Statement of fulvestrant sharing the same mechnism of action as amecenestrant was added. Cross over design content was removed.	This content was added to provide further clarify of the mechanism of action of fulvestrant.
Section 6.2.1 Starting dose and dose levels	Footnote a was added and subsequent footnotes realphabetized. Footnote d was updated.	Footnote a was added and footnote d was modified in order to provide consistency with the clinical trial summary.
Section 6.3 Maximum Adminstrated Dose/Maximum Tolerated Dose	Arm #4 and #5 (Parts H and J) were included.	This content was added to reflect the new study design.
Section 6.2.2 Dose escalation Arms #1, #2, #4, and #5 (Parts A, C, H, and J) and Safety Run-in Arm #3 (Part F) strategy	Corresponding Arm #4 (Part H) and #5 (Part J) added to the title. Statement referencing BID regimen for Part A and Part C was removed. Sample size for Arm #3 (Part F),Arm #4 (Part H) and Arm #5 (Part J) was updated to 12 patients.	This content was added to reflect the new study design.

Section # and Name	Description of Change	Brief Rationale
Section 6.5 Dose delays modification	New content and Table 8 for everolimus and abemaciclib were added.	This content was added to reflect the new study design and dose level reduction for everolimus and abemaciclib.
Section 6.5.2 Arm #3 Dose modification in Parts F and G	Details on hypersensitivity was added. Table 12 content and footnotes were modified.	New content was added in order to further describe hypersenstivity symptoms and dose modifications for CTCAE grades.
Section 6.5.3 Arm#4 Dose modification in Parts H and I	New section added for Arm #4 Parts H and I. Tables 13 and 14 were added and subsequent tables were renumbered.	This content was added to describe dose modifications and management in Arm #4 Part H and I.
Section 6.5.4 Arm #5 Dose modification in Parts J and K,	New section added for Arm #5 Parts J and K. Table 15 and 16 were added and subsequent tables were renumbered.	This content was added to describe dose modifications and management in Arm #5 Part K and J
Section 6.7 Guidelines for management of adverse events	Examples of clinical data available for amcenestrant was added.	This content was added to provide examples of clinical data available.
Section 6.9 Interim analysis and Section 13.10 Interim analysis	Interim analysis for Arm #2 and #4 Parts D and G and BID regimen for Arm #1 Part B was removed.	This content was removed because an interim analysis is no longer planned for these study parts.
Section 8.4 Storage conditions and shelf life	Content regarding temperature storage was removed.	Specific temperature storage was removed because compound will be managed according to the Pharmacy Manual provided by the Sponsor.
Section 8.5.1 Treatment accountability and compliance	Text regarding everolimus and abemaciclib added.	The new text was included to specifiy all unused medication from the study must be returned at the end of treatment.
Section 8.6 Concomittant treatment	Content regarding concomittant medications in treatment arms updated. Concomittant medications related to new study parts added.	This content was updated to include new information regarding concomittant medications in the treatment arms.
Section 9.2.1 Sampling time and sample blood volume, Section 9.2.2 Pharmacokinetic sample handling procedure and Section 9.5 Sampled blood volume	New content was added in tables for blood samples and volume for Arm #4 and #5 Parts H, I, J, and K. Subsequent table numbers renumbered.	This content was added in order to show sampled blood volume per patient and sample handling in Arm #4 and #5 Parts H, I, J, and K.
Section 9.2.3 Bioanalytical method, Section 9.2.5 Pharmacokinetic parameters, Section 13.9.5 Analyses of pharmacokinetic and pharmacodynamic variables	New content added for bioanalytical methods for everolimus and abemaciclib and its metabolites.	This content was added to include additional bioanalytical methods due to the new study design.
Section 9.5 Sampled blood volume	PD sample (cfDNA for mutational profiling) was updated for Arm #3 Parts F and G.	The table was updated to reflect the 4 samples needed for cfDNA mutational profiling.
Section 10.5.5 Adverse event of special interest and Section 10.6 Obligations of the sponsor	Details on investigation in case of ALT ≥Grade 3 and new AESI photosensitivity were added.	The list of AESIs was updated in order to provide additional details on AEs relevant to the study.

Section # and Name	Description of Change	Brief Rationale
Section 12.2 Baseline evaluation	Text regarding *PIK3CA* mutation determination for Arm #3 (Part F and G) was removed.	Content removed due to redundancy. It was mentioned in a separate portion of the protocol.
Section 12.2 Baseline evaluation, Section 12.4.4 Cycle 1, between Day 11 and Day 15 (Arm #1 Part A only)	Content modified to show ^{18}F-FES-PET scan will be done for Part A QD and BID and FDG PET/CT will only be done for Part A BID.	This content was added in order to clarify which scans would be done for Part A QD and BID.
Section 12.2 Baseline evaluation and Section 12.6 End of treatment visit (to be performed between 22 and 30 days after the last administration of the study treatment)	Laboratory assessment to include Parts H and I.	This content was added to include assessments done in Parts H and I.
Section 12.5.5 Subsequent cycles (up to and including C6), Day 15 (±2 days) and Section 12.5.6 Subsequent cycles (starting from C7 and onwards), Day 1 (±2 days)	New section added for subsequent cycles. Following sections were renumbered.	This content was added in order to provide additional subsequent cycles during the study.
Section 12.5.6.2 Additional tests for Arms #3 and #4 (Parts F, G, H, and I)	New section added for additional tests done for Arms #3 (Parts F and G) and #4 (Parts H and I). Subsequent sections renumbered.	This section was added in order to reflect the new study design.
Section 13.9.5.1 Analyses of pharmacokinetic variables	Content regarding everolimus and abemaciclib added.	This content was added to reflect the new study design.
Section 13.9.5.2 Analyses of pharmacodynamic variables	New section added for analyses of pharmacodynamic variables. Subsequent sections renumbered.	This section was added for organization purposes and to provide a separate section regarding pharmacodynamic variables.
Section 18 Bibliographic references	New reference added and updated.	This section was updated to include new sources referenced in the body.
Section 19 Appendix E List of CYP3A4 Prohibited Modulators	Content updated to reflect strong/moderate CYP3A4 inhibitors are not permitted in Arm #4.	This section was modified to prevent a drug drug interaction in Arm #4.
Section 19 Appendix F List of CYP substrate with a narrow therapeutic range and list of substrates mainly metabolized by CYP3A/2B/2C/UGT	Table for drugs mainly metabolized by CYP3A, CYP2Cs and/or UGTs updated.	This content was updated to show reflect a current list of drugs that are sensitive substrates of CYP3A, CYP2Cs and/or UGTs.
Section 19 Appendix H In vivo inhibitors of P-gp probes	New appendix added. Subsequent appendix re-alphabatized.	This new appendix was added to include a list of in vivo inhibitors of P-gp probes.

In addition, other minor editorial changes (eg, grammatical, stylistic, and minor typographical error corrections) were implemented throughout the protocol.

Amendment [08] [30 October 2020]

This Amended Protocol 08 (Amendment 08) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

The objective of the amendment is to:

1. Modify description of alpelisib formulation throughout the protocol in accordance with the change in supply from the commercial material to the clinical trial material.
2. Remove study Part E with midazolam. The part E of the study was planned to assess the interaction of SAR439859 at 200 mg and 400 mg with midazolam. Considering that results obtained in a separate study in healthy volunteers are satisfactory for the midazolam and SAR439859 interaction, Part E of the TED14856 study is closed and, therefore, removed from the objective of this study.
3. Modify study design of Part F (combination with alpelisib) from dose escalation to the safety run-in phase which will explore combination of the approved (standard) dose of alpelisib (300 mg QD) with SAR439859 200 mg QD dose as selected dose for combination therapy of SAR439859 and other agents, with an option, if needed, to test additional doses of SAR439859 (eg, 300 mg QD or 400 mg QD etc.) depending on safety and pharmacokinetics profile of the combination. SAR439859 400 mg QD was established as the recommended dose for monotherapy in heavily pretreated patients; however, the dose of 200 mg QD of SAR439859 in combination with targeted therapy may be optimal dose based on the pharmacodynamic results observed so far on ^{18}F-FES-PET scans with almost 90% of ER inhibition and, therefore, the goal is to confirm this dose in combination with alpelisib (Part F).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Study name AMEERA-1 was added on title page.	Title page was updated to provide the study's name.
Global	Part E Midazolam has been removed throughout the study protocol and subsequent sections, tables, and footnotes were renumbered accordingly. Dose escalation of Part F was changed to safety run-in throughout the document.	This content was updated to reflect new study design and provide clarity.
Clinical Trial Summary and Section 4.4.4 Part D (dose expansion, combination with palbociclib), Section 4.4.6 Part G (dose expansion, combination with alpelisib), and Section 6.2.1 Starting dose and dose levels	Sentence "Intra-patient dose escalation or re-escalation of any study drug is not allowed" was added.	This content was added in order to provide clarity in the study design.
Clinical Trial Summary and Section 6.2.1 Starting dose and dose levels	In Part A , dose re-escalation will not be permitted.	This content was updated in order to provide clarity in the study design.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary and Section 5.1 Primary Objectives	Safety run-in Part F primary objective was modified. In Part B, ICR was added.	This content was modified in order to provide clarity.
Clinical Trial Summary and Section 6.1 Description of the Study	Clarification of study design was made.	This content was added to provide clarity and consistency with the new study design.
Clinical Trial Summary and Section 6.2.1 Starting Dose and Dose Levels	Part A additional dose exploration and Part F study description was modified. New decision tree was added. Dose level in Table 4 and Table 3 were removed. Subsequent table numbers renumbered.	This content was modified to provide consistency in study design. Decision tree was added in order to provide further details about the study design.
Clinical Trial Summary and Section 6.8.1 Duration of Study Participation for Each Patient	Expected enrollment period, cycles of treatment, and COD were updated.	This content was updated to reflect new study design.
Clinical Trial Summary and Section 7.2 Inclusion Criteria	I06 and I12 was modified.	This content was modified to provide new information/clarification and consistency in the study design.
Clinical Trial Summary and Section 7.3 Exclusion Criteria	Part E exclusions are removed per amendment 08. E13, E20, E31, and E33 were modified. New exclusion criteria E34 was added.	This content was modified to provide clarification and consistency in the study design. A new exclusion criteria was added as per requirement for Parts F and G.
Clinical Trial Summary and Section 8.1.2.1 SAR439859	In Part F and G, dose modified from 400 mg to 300 mg QD. Statement added to address taking study drugs in a fed or unfed condition.	The dose was modified to reflect changes in the design plan. New information added in order to explain which study drugs are to be taken with or without food.
Clinical Trial Summary, Section 8.1.1.3 Alpelisib and Section 8.1.2.3 Alpelisib	Alpelisib clinical supply was modified.	This content was modified to reflect alpelisib clinical supply type in the study.
Clinical Trial Summary endpoints	Specification for primary endpoints in part A, C and F was added if additional patients were enrolled.	This content was added to provide consistency in study design.
Clinical Trial Summary and Section 13.1.5 Sample Size of the Safety Run-in Part for SAR439859 in Combination with Alpelisib (Part F)	Header and study design updated.	This content was modified and updated to be consistent with the new study design.
Section 1.1: Graphical Study Design - Dosing Scheme	Part F dosing scheme was updated.	This content was updated to reflect new study design.
Section 1.2 Graphical Study Design – Study Scheduling	PIK3CA testing Period (F&G) was added to the diagram and new footnote added.	This content was added as new information for pre-screening for parts F and G only.
Section 1.3: Study Flowchart	Study flowchart updated. Footnote bb and dd were removed and subsequent footnotes were reordered.	This content was added and updated to provide clarity and consistency within the study design.

Section # and Name	Description of Change	Brief Rationale
	Footnotes g, h, i, l, r, y, z aa, and dd were updated. New footnotes, ee and ff, were added.	
Section 1.4.1 Part A	Analysis for pharmacodynamics in plasma was updated. New row for saliva collection added and footnote e updated.	This content was added to provide clarity and consistency in study design.
Section 1.4.2.1 Part B Full PK Sampling	Analysis for pharmacodynamics in plasma was added. New footnote and row for saliva collection added. Footnote f was updated.	This content was added to provide clarity and consistency in study design.
Section 1.4.2.2 Part B Sparse PK Sampling	Analysis for pharmacodynamics in plasma was added. New footnote for saliva collection added. Footnote d was updated.	This content was added to provide clarity and consistency in study design.
Section 1.4.3.1 Part C and D Full PK Sampling and Section 1.4.4.1 Full PK Sampling (Part F and G)	Analysis for pharmacodynamics in plasma was added. New footnote and row for saliva collection added.	This content was added to provide clarity and consistency in study design.
Section 1.4.3.2 Part D Sparse PK Sampling	Analysis for pharmacodynamics in plasma was added. Footnote c was updated.	This content was added and updated to provide clarity and consistency in study design.
Section 1.4.4 Part F and G	Clarification made on analysis used for Part F and G.	This content was added to provide clarity and consistency in study design.
Section 1.4.4.2 Sparse PK sampling (Remaining patients in Part G)	Analysis for pharmacodynamics in plasma and footnote related to it was updated.	This content was added to provide clarity and consistency in study design.
Section 4.1 Introduction	BYLieve study was added. References were updated accordingly.	This content was added to provide clarity.
Section 4.3.1 Preclinical Data	Text was added related to BCRP sensitive substrates.	This content was added to provide consistency.
Section 4.4.5 Part F (Safety run-in phase with alpelisib)	Additional content on the BYLieve study, additional text regarding exploring of SAR439859, and alpelisib doses were added.	This content was added to provide more information on adverse events and exploration of SAR439859 and alpelisib doses.
Section 6.3 Maximum Adminstration dose/Maximum Tolerated Dose	MAD definition updated.	This content was updated to provide consistency.
Section 6.2.2 Dose Escalation (Parts A and C) and Safety run-in (Part F) Strategy	Header title was modified and enrollment plan of patients in Part F was updated.	This content was modified to improve clarity and provide new information on enrollment plan.
Section 6.5 Dose delays/Modification	Sentence “Therefore, no cycle delay is defined in any study parts” was removed.	This content was removed to provide consistency.
Section 6.5.2 Dose Modification in parts F and G	Clarification regarding dose modifications was made in table 10. Footnote b was updated.	This content was added to provide clarity and consistency in study design.

Section # and Name	Description of Change	Brief Rationale
Section 6.6 Expansion Cohorts to Confirm the Maximum Tolerated Dose	Deleted text "+ additional 34 if randomization is used in Part G; total 339".	This content was deleted in order to provide consistency in the study design.
Section 6.8.1 Duration of Study Participation for Each Patient	Statement added for testing PIK3CA status in patients who have never undergone PIK3CA testing for parts F and G only.	This content was added to provide additional information regarding eligibility in the study for parts F and G only.
Section 8.1 Investigational Medicinal Product	New statement added to address direct to patient delivery option. Appendix I added as a reference.	This content was added to provide information regarding the study drug's Direct to Patient delivery option.
Section 8.4 Storage conditions and shelf life	Storage condition for alpelisib was updated.	This content was modified based on alpelisib's storage conditions.
Section 8.6 Concomitant Treatment	Drug-drug interactions with alpelisib were described. Appendix G added as a reference.	Appendix G and drug drug interactions with aleplisib was added to provide caution for drug interactions.
Section 9.2.2 Pharmacokinetic sample handling procedure	Part G was added to Table 21 header.	Table 23 was removed in order to reflect new study design. The header for Table 21 was updated to include Part G to provide consistency within the study design.
Section 9.2.3 Bioanalytical Method	Table 22 header was modified.	This content was updated in order to provide consistency with new study design.
Section 9.3.1 Optional drug Metabolizing Enzymes and Transporters DNA sample	Clarification of sampling used to investigate phArmacogenitic variability related to ADME of SAR439859 on PK/PD.	This content was updated to provide clarity.
Sectin 9.4.3 Mutational Profiling in Circulating Free DNA	ESR1 pathway added to list of genes.	The pathway was added to provide an example of an additional gene that will be analyzed.
Section 9.4.4 Tumor biopsy to assess Estrogen Receptor Degradation (Part A BID, Part B, F and G)	Added part G to header.	This content was updated to be consistent with study design.
Section 9.5 Sampled Blood Volume	Removed PK sample SAR439859 (sparse PK). Updated PD sample (estradiol) volume per sample, volume per patient, total number of samples and footnote c.	Table was updated to provide consistency with the study design.
Section 9.7.1 Criteria for response (antitumoral activity)	Tumor assessment updated.	This content was updated to provide additional information and clarification on when tumor assessment will occur.
Section 10.5.5 Adverse Event of Special Interest	A new AESI was added.	This content was modified to provide an additional AESI in the study.
Section 10.5.6 Laboratory Abnormalities	DLTs were added as laboratory abnormalities.	This content was modified to provide further clarification on what should be considered a laboratory abnormality.
Section 11.1.2 Handling of Patients After Permanent Treatment Discontinuation	Clarification of handling patients after permanent discontinuation made.	This content was updated to be consistent with study design.

Section # and Name	Description of Change	Brief Rationale
Section 11.3 Criteria for Temporarily Delaying	This is a new section to Amended Protocol 08 for contingency measures for temporarily delaying study.	This content was added to provide contingency measures.
Section 12.2 Baseline Evaluation	Clarification for Part F and G added to coagulation assessment and in blood chemistry. Additional content provided for PIK3CA Testing ICF for Part F and G.	This content was added to provide clarity and consistency with study design.
Section 12.4.1 Cycle 1, Day 1	Updated PK/PD blood sample collection details.	This content was updated in order to provide clarity.
Section 12.5.4.1 Every 8 weeks	Tumor evaluation and details of Hemoglobin A1C assessment was updated.	This content was updated to provide additional information.
Section 12.6 End of treatment visit (to be performed between 22 and 30 days after the last administration of the study treatment	Laboratory assessments for coagulation and blood chemistry updated.	This content was updated to provide additional details regarding coagulation and blood chemistry.
Section 12.8 Post Study Cut-Off Period	Clarification of post study treatments were made.	This content was modified in order to clarify the post study treatment and follow up.
Section 13.1 Determintation of Sample Size	Clarification of sample size was made.	This content was modified to clarify and provide the number of patients that will be enrolled.
Section 13.1.5 Sample size of the safety run-in part for SAR439859 in combination with alpelisib (Part F)	Header and number of patients were updated. Reference to Section 6.2.1 decision tree added.	This content was updated in order to provide further information and consistency for Part F.
Section 15.6 Data Quality Assurance	This is a new section to Amended Protocol 08 for monitoring source data.	This content was added to provide monitoring details.
Section 18 Bibliographic references	Updated references.	This content was updated to be consistent with the new added reference.
Appendix E List of CYP3A4 and CYP2C8 prohibited modulators	Weak CYP3A inhibitors and weak CYP3A inducers were removed from the appendix.	This content was removed because Part E was cancelled.
Appendix I Contingency Measures for a Regional or National Emergency that is Declared by a Governmental Agency	New appendix for Amended Protocol 08 added for contingency measures for a regional or national emergency that is declared by a governmental agency.	This content was added to provide contingency measures.
Appendix G List of BCRP Inhibitors, CYP2C9 Substrates and P-gp, BCRP and OAT3 Substrates	New appendix for Amended Protocol 08 added for BCRP inhibitors, CYP2C9 substrates and P-gp, BCRP and OAT3 substrates. Susequent appendix numbers were renumbered accordingly.	This content was added to provide a list of concomitant medications that should be avoided.

Amendment 07 [03 April 2020]

This amended protocol 07 (Amendment 07) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

The objective of the amendment is to:

1. Modify treatment options in Part E (midazolam drug-drug interaction part) after Cycle 1 in order to facilitate recruitment, ie, from Cycle 2, investigators will have the option to either select the RD of monotherapy (ie, SAR439859 400 mg QD single agent) or the RD of the combination therapy with palbociclib (ie, SAR439859 200 mg QD + palbociclib 125 mg QD) or in combination with alpelisib (at RD for Part G).

2. Explore the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of the combination of SAR439859 with alpelisib (PIQRAY®).

Alpelisib (PIQRAY®) has recently been approved by the FDA for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative, *PIK3CA*-mutated, advanced or metastatic breast cancer following progression on or after an endocrine therapy.

In the newly added study cohorts (Parts F and G) of this study, alpelisib will be used at the approved dose level, 300 mg QD by oral route (as per label, permitted dose reductions, if needed) in combination with SAR439859. Two dose levels of SAR439859: 200 mg QD and 400 mg QD by oral route will be tested. The effect of SAR439859 on alpelisib's PK will be explored with a first step with 3-day dosing of alpelisib alone followed by continuous co-administration with SAR439859 in 28-day cycles. This combination will be investigated in dose escalation (Part F) and dose expansion (Part G) study parts. Dose escalation will explore safety, PK and PD profile of the SAR439859 and alpelisib combination, and dose expansion (Part G) will assess safety, tolerability and the preliminary antitumor activity of the combination. Upon completion of the dose escalation, a decision from the Study Committee about recommended dose for dose expansion will be made based on safety, PK and PD profile of the combination. A single-sequence cross-over design is proposed to determine the effect of SAR439859 on alpelisib between two timepoints in Cycle 1 Day 3 (alpelisib alone) and Cycle 1 Day 22 (alpelisib in combination with SAR439859). This will be done for each dose level of SAR439859.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page and tabulated clinical trial summary	Changed palbociclib to other anti-cancer therapies in the title.	To be consistent with the updated study design.
Tabulated clinical trial summary, Section 1.1 Graphical study design -Dosing scheme, Section 1.2 Graphical study design - Study scheduling, Section 1.3 Study flow chart, and Section 1.4.5 Part F and G PK sampling, and Section 4.4.6 Part F (dose escalation, combination with alpelisib), Section 4.4.7 Part G (dose expansion, combination with alpelisib), Section 6.10 Study committees	Updates made to include Part F and G.	Details added for the new study design.
Tabulated clinical trial summary, Section 1.1 Graphical study design -Dosing scheme, Section 1.2 Graphical study design - Study scheduling, Section 1.3 Study flow chart, Section 1.4.4, Part E PK sampling, Section 6.2.1 Starting dose and dose levels, and Section 8.1.2.1 SAR439859	Added new dosing options after Cycle 2 in Part E.	To be consistent with the updated study design.
Tabulated clinical trial summary, and Section 5.1 Primary Objective	Added new objectives for Part F and G.	Details added for the new study design.
Tabulated clinical trial summary, Section 5.2 Secondary objectives	Updated this section to include Part F and G.	Details added for the new study design.
Tabulated clinical trial summary, Section 5.3 Exploratory objectives	Updated this section to include Part F and G.	Details added for the new study design.
Tabulated clinical trial summary, Section 6.1 Description of the study, Section 6.2.1 Starting dose and dose levels, Section 6.2.2 Dose escalation strategy, Section 6.3 MAD/MTD and Section 8.1.1.3 alpelisib, Section 8.1.2.1 SAR439859 and Section 8.1.2.4 Alpelisib	Added details of SAR439859 and alpelisib administration in Part F and G.	To assess the new study part as described above.
Tabulated clinical trial summary, Section 9.4.2 Estrogen receptor 1 gene mutation status, Section 9.4.3 mutational profiling in cfDNA and Section 9.4.4. tumor biopsy to assess ESRD	Updates made to include Part F and G.	Details added for the new study design.
Section 4.1 Introduction	Updated the Introduction with alpelisib information.	To be consistent with the new study design.
Section 6.5.2 Dose delays and modifications in Parts F and G	Added alpelisib dose delays.	For simplification and for alignment with alpelisib label.
Tabulated clinical trial summary and Section 6.8.1 Duration of study participation for each patient	Updated the enrolment period time and included cycle durations for Part F and G.	Based on the new study design for Part F and G.
Tabulated clinical trial summary and Section 7.2 Inclusion criteria	Modified I01.	Modified as per alpelisib label.
Tabulated clinical trial summary and Section 7.2 Inclusion criteria	Modified I05.	For clarification of inclusion criteria specific for Part G.
Tabulated clinical trial summary and Section 7.2 Inclusion criteria	Modified I06 to include Part F.	For clarification.

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary and Section 7.2 Inclusion criteria	Added new inclusion criteria I12.	As per requirement in Parts F and G.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to the disease	Added new details to Exclusion Criteria E13 for Part G.	For clarification on the exclusion criteria specific for Part G.
Tabulated clinical trial summary, Section 7.3.2 Exclusion criteria related to the disease	Modified Exclusion criteria E20.	For consistency with other SAR439859 studies.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to disease	Modified E22, E23 and E24.	For clarification.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to disease	Added new exclusion criteria E30, E31, E32 and E33 for Part F and G only.	As per the dosing label for alpelisib.
Tabulated clinical trial summary	Updated expected number of sites.	Change in sample size.
Section 8.6 Concomitant treatment	Updated section to include prohibited medication as per alpelisib label and update the prohibited medications for SAR439859.	As per new study design for Part F and G.
Tabulated clinical trial summary, Section 1.4.5.1 and 1.4.5.2 PK and PD flow chart, Section 9.2.1 Sampling time and sample blood volume, Section 9.2.2. PK sample handling procedure, Section 9.2.3 Bioanalytical method, Section 9.2.5 PK parameters, Section 9.5 Sampled blood volume, Section 13.4.5 Analyses of PK and PD variables	Updated the PK sampling schedule to include Part F and G and added PK parameters for Part F and added alpelisib bioanalytic methods.	To include the Part F and G study design.
Tabulated clinical trial summary and Section 9.1.1 DLT	Added new DLT criteria for Part F only.	As per alpelisib label.
Tabulated clinical trial summary, Section 8.1.1.3 alpelisib and Section 8.1.2.4 Alpelisib,	Added alpelisib administration, formulation.	New details added as per study design for Part F and G.
Tabulated clinical trial summary, Section 6.6 Expansion cohorts to confirm the MTD, Section 13.1 Determination of sample size, Section 13.1.6 Sample size of the dose escalation phase for SAR439859 in combination with alpelislib (Part F) and Section 13.1.7 Sample size expansion phase combination with alpelisib (Part G)	Updated the sample size number to include Part F and G.	To include Part F and G new study design.
Section 1.3 Flowchart and Section 12.1 Visit Schedule	Changed visit structure from Cycle 7 onwards to only have monthly visit.	To simplify study visits requirement for patients after first 6 cycles of treatment as per patients' feedback.
Section 12.2 Baseline evaluation, Section 12.4. During the treatment period in Cycle 1 and Section 12.5 During subsequent cycles	Updates made to include Part F and G.	Details added for the new study design.
Section 6.9 Interim analyses and Section 13.5 interim analyses	Updated with Part G information.	To align with the new study design.
Section 13.2 Patient description, and Section 13.4.2 Extent of IMP exposure	Added Part F and G.	To align with the new study design.

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary and Section 13.4.5 Analyses of PK and PD variables	Added details for alpelisib.	To align with new study design for Part F and G.
Section 18 Bibliographic references	Updated references.	Consistent with the new added text.
Global	Added clarifications for testing in different parts of the study.	To improve clarity.

Amendment 06 [02 October 2019]

This amended protocol (amendment 06) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

This amendment has been issued to implement safety monitoring measures following identification of a new risk related to palbociclib. Palbociclib may increase the risk of interstitial lung disease (ILD)/ pneumonitis as per recent FDA communication and the United States Prescribing Information (USPI) update in September 2019 and the Canada Product Monograph of Palbociclib (IBRANCE®) update in August 2019.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 6.5 Dose delays and modifications	Addition of measures for management of suspected or confirmed ILD/Pneumonitis for patients treated in Part C and D.	Implementation of safety monitoring measures following identification of new risk identified for palbociclib.

Amendment [5] [02 August 2019]

This amended protocol (amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

This amendment has two objectives:

1. To add a new study part (Part E) which will assess the effect of SAR439859 on CYP3A enzyme activity by using midazolam as a probe in a new cohort of patients. The selection and assessment criteria for Part E will remain the same as in Part A and B but with the omission of the pilot food effect as well as FES-PET and FDG-PET scan.
2. To add a new option and to modify the selection criteria in Part D (details below).

Part D of this study has been modified and simplified by adding a randomized two-Arm option (potentially in replacement of the single Arm currently present in the protocol), depending on a decision at the end of Cycle 1 of Part C. The aim of Part C is to select the recommended dose of the SAR439859 and palbociclib combination based on the safety and pharmacokinetic (PK) data.

Two doses of SAR439859, 200 mg and 400 mg combined with one dose of palbociclib 125 mg have been studied in Part C in the first 6 patients. There was no DLT observed for these two doses and the combination was well tolerated. The preliminary PK results from Part C in these patients (3 patients per dose level) indicated a possible decrease of palbociclib exposure when given with SAR439859. A decision was made by the Study Committee to treat 6 additional patients at the same two dose levels (3 patients per dose) in order to have a supplementary PK data to analyze this potential drug-drug interaction. When the last patient (ie, 12th patient) in Part C completes Cycle 1, the Study Committee will determine at least 1 RD for Part D primarily based on DLTs, overall safety at all cycles (early and late toxicities), PK and antitumor activity data. The Study Committee may decide to select more than one RD for evaluation in Part D. Data from Part A and Part B may also be considered as applicable in decision making of the RD dose for Part D. If more than 1 dose is selected for Part D, patients will be manually randomized to each dose.

The selection criteria for Part D have also been revised. The current Part D selection criteria allows patients with multiple prior therapies and it is anticipated that allowing number of prior therapies will jeopardize the chance to evaluate an appropriate efficacy of the combination. Therefore the following selection criteria will be added for Part D only:

- No more than 3 prior lines of therapy in the metastatic setting: no more than two hormonal therapies and no more than 1 line of chemotherapy.
- The following prior therapies for advanced disease are not allowed: CDK4/6 inhibitors, PI3K inhibitors and mTOR inhibitors

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary, Section 1.1 Graphical study design -Dosing scheme, Section 1.2 Graphical study design - Study scheduling, Section 1.3 Study flow chart, Section 1.4.3 Parts C and D, and Section 1.4.3.2 Part D sparse PK sampling, and Section 4.4.4 Part D (dose expansion, combination with palbociclib)	Updates made to Part D.	Updated study design based on the results of Part C as described above.
Tabulated clinical trial summary, Section 1.1 Graphical study design -Dosing scheme, Section 1.2 Graphical study design - Study scheduling, Section 1.3 Study flow chart, and Section 1.4.4 Part E PK sampling, and Section 4.4.5 Part E (midazolam drug drug interaction)	Updates made to include Part E.	To assess the effect of SAR439859 on CYP3A enzyme activity by using midazolam as a probe.
Tabulated clinical trial summary, and Section 5.1 Primary Objective	Updated primary objective for Part D and added new objective for Part E.	Details added for the new study design.
Tabulated clinical trial summary, Section 5.2 Secondary objectives	Updated this section to include Part E and new Part D study design.	For consistency.
Tabulated clinical trial summary, Section 6.1 Description of the study, Section 6.2.1 Starting dose and dose levels, and Section 8.1.2.1 SAR439859	Added details of the SAR439859 administration in Part E.	To assess the new study part as described above.

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary and Section 6.8.1 Duration of study participation for each patient	Updated the enrolment period time and the cut-off-date for Part D.	Based on the new study design for Part D.
Tabulated clinical trial summary and Section 7.2 Inclusion criteria	Modified I05.	To be consistent with the new selection criteria for Part D.
Tabulated clinical trial summary and Section 7.2 Inclusion criteria	Removed I12 and added it as a part of I06.	For clarity.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to the disease	Removed E12.	Preclinical toxicity data with SAR439859 has not shown signal of endometrial disorders.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to the disease	Modified Exclusion criteria E20 to include probenecid.	For consistency with other SAR439859 studies.
Tabulated clinical trial summary, Section 1.4.1 Part A and Section 7.3.2 Exclusion criteria related to the disease	Modified E21.	To include Part A (BID) in 4B-OH cholesterol test.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to disease	Modified E22.	To improve clarity.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to disease	Added new exclusion criteria E25 for Part D only.	Based on the new selection criteria for Part D as discussed above.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to the disease	Added new exclusion criteria E26, E27, E28 and E29 for Part E only.	As per the dosing label for midazolam.
Tabulated clinical trial summary	Updated expected number of sites.	Change in sample size.
Section 1.3 Study flow chart, Section 6.8.1 Duration of participation for each patient and Section 12.6 end of treatment visit	Added details on follow-up after further therapy is initiated before D22 or after study treatment discontinuation.	For clarity.
Section 8.6 Concomitant medication	Updated section to include prohibited medication as per midazolam label and update the prohibited medications for SAR439859.	As per new study design for Part E.
Tabulated clinical trial summary, Section 1.4 PK and PD flow chart, Section 9.2.1 Sampling time and sample blood volume, Section 9.2.2. PK sample handling procedure, Section 9.2.3 Bioanalytical method, Section 9.2.5 PK parameters, Section 9.5 Sampled blood volume, Section 13.4.5 Analyses of PK and PD variables	Updated the PK sampling schedule to include Part E and added PK parameters for Part E and added midazolam bioanalytic methods.	To include the Part E study design.
Tabulated clinical trial summary, Section 7.3.2 exclusion criteria related to disease and Section 12.2 Baseline evaluation	Added GGT to E17 and correspondingly added GGT testing at baseline.	Based on new safety findings.

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary, Section 8.1.1.3 midazolam, Section 8.1.2.3 Midazolam, Section 12.3 Before first IMP administration	Added Midazolam administration, formulation and storage conditions.	New details added as per study design for Part E.
Tabulated clinical trial summary, Section 6.6 Expansion cohorts to confirm the MTD, Section 13.1 Determination of sample size, Section 13.1.4 Sample size of the expansion phase for SAR439859 in combination with palbociclib (Part D) and Section 13.1.5 Sample size of midazolam drug-drug interaction (Part E)	Updated the sample size number to include Part E and new sample size of Part D.	To include Part E and Part D new study design.
Section 1.4.2.2 Part B sparse PK sampling, Section 1.4.3.1 Part C and D full PK sampling, Section 1.4.3.2 Part D sparse PK sampling, Section 1.4.4 Part E PK sampling and Section 9.4.5 Estradiol	Serum estradiol sampling added.	To explore possible influence of circulating levels of estradiol on preliminary efficacy of SAR439859.
Section 13.2 Patient description	Added Part E (midazolam drug-dug interaction).	To align with the new study design.
Section 13.4.4.1 Dose limiting toxicities	Updated the analyses section.	To improve clarity.
Section 6.9 Interim analysis, and 13.5 Interim analyses	Updated requirements for interim analyses in Part D.	Based on the new study design and sample size, the interim analysis has been modified.
Appendix E List of CYP3A4 inhibitors and CYP2CA inducers	Modified and added weak CYP3A inhibitors, inducers and moderate CYP2C8 inducers.	To align with the addition of Part E of the study and new requirements for midazolam administration.
Global	Added clarifications for testing in different parts of the study.	To improve clarity.

Amendment [4]: [29-Jan-2019]

This amended protocol (amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

Part A of the current study consisted of dose escalation of SAR439859 starting from 20 mg to 600 mg once daily (QD). A total of 16 patients have been treated in Part A of the study. No DLTs were observed and the study drug has been well tolerated; the recommended dose for further exploration was determined at 400 mg QD based on pharmacokinetic (PK) (mainly, C_{trough} at 24h) and pharmacodynamic results (≥90% inhibition of estrogen receptor as per ^{18}FES-PET scan).

The objective of this amendment is to assess the new schedule of SAR439859 administration at the same dose intensity as the highest tested dose of 600 mg QD but given as 300 mg twice daily (BID). This new schedule is an extension of the dose escalation Part A of the study.

Pharmacokinetic data obtained from all patients treated in Part A (n=16) were analyzed using a preliminary population 2-compartment PK model with lag time and showed that a BID dosing regimen will modify the PK plasma concentration-time profile of SAR439859 for the same total daily dose. The C_{trough} concentrations are expected to be increased by around 1.8-fold and C_{max} is expected to be decreased by 1.7-fold, whilst maintaining the same AUC over 24-hour period at steady-state.

Finally, from PK simulation, it is anticipated that in order to optimize the likelihood of a maximal target inhibition, an administration of 300 mg BID would have a higher probability of ER saturation than 400 mg and 600 mg QD dose regimens as well as 200 mg BID by increasing median C_{trough} up to about 900 ng/mL and reducing the peak and trough fluctuations. The schedule of 300 mg BID could potentially be the recommended dose for patients who have progressed after receiving several lines of hormonal therapies, either as monotherapy or in combination with targeted agents.

It is expected that SAR439859 300 mg BID will be well tolerated since the daily dose of 600 mg has already been assessed with a favorable safety profile. In addition, C_{max} levels with 300 mg BID will be decreased compared to 600 mg QD, potentially reducing the risk of adverse events (AEs) that are correlated with C_{max}. However, in case of an occurrence of DLTs during the exploration of the DL5bis (300 mg BID) dose level, an assessment of the DL4bis (200 mg BID) will be done as per the evaluation criteria used for other previously tested Part A dose levels (ie, evaluation of DLT occurrence during the first cycle, PK results and ^{18}FES-PET scan results).

The compliance will be analyzed in order to assess the impact of a BID dosing regimen compared to a QD one. Moreover, the omission of one dose of SAR439859 when given once a day would be expected to have a negative impact on the 24-hour coverage of the estrogen receptors whereas if one capsule of the BID regimen is omitted, there would be less impact on the plasma concentration level, resulting in a decreased impact on the estrogen receptor coverage.

This new schedule is now detailed in Part A of the protocol; the selection and assessment criteria will remain the same as in Part A but with the omission of the pilot food effect testing for which sufficient information were collected from the once-daily dosing regimen. The BID dose at 600 mg will be split in two intakes (without omission on Day 2): 300 mg taken two times a day, 12 hours apart (ie, 2 x 300 mg) ±1 hour and will be taken independent of food conditions.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Graphical study design -Dosing scheme, Section 1.2 Graphical study design - Study scheduling, Section 1.3 Study flow chart, and Section 1.4 PK and PD flow chart, and Section 4.4.1 Part A (dose escalation, monotherapy SAR439859)	Updates made to include the BID dosing regimen.	To further assess the dosing regimen in a BID schedule.
Tabulated clinical trial summary, Section 4.4.2 Part B (dose expansion monotherapy SAR439859), Section 6.6 Expansion cohorts to confirm the MTD, Section 6.9 Interim analysis, Section 13.1.2 Sample size of the expansion phase for SAR439859 as monotherapy (Part B) and Section 13.5 Interim analysis	Added details of a potential BID regimen administration in Part B including sample size updates and an interim analysis in Part B.	For clarification and consistency of the BID across sections.
Tabulated clinical trial summary, Section 4.4.3 Part C (dose escalation combination with palbociclib), Section 6.2.1 Starting dose and dose levels and Section 6.2.2. Dose escalation strategy (Parts A and C)	Added clarification that a BID dosing regimen could be explored in Part C.	For clarification and consistency of the BID across sections.
Tabulated clinical trial summary, Section 5.3 Exploratory objectives, Section 9.4.4 Tumor biopsy to assess estrogen receptor degradation	Added the biomarker Bcl-2 to the exploratory objective.	To evaluate other breast cancer biomarkers over time.
Tabulated clinical trial summary and Section 6.2.1 Starting dose and dose levels, Section 6.2.2. Dose escalation strategy (Parts A and C), Section 8.1.2.1 SAR439859	Added details of the BID dose regimen in Part A.	To assess a new dosing schedule as described above.
Tabulated clinical trial summary and Section 7.2 Inclusion criteria	Modified Inclusion criteria I01.	For clarification.
Tabulated clinical trial summary and Section 7.2 Inclusion criteria	Modified Inclusion criteria I05.	For clarification.
Tabulated clinical trial summary and Section 7.2 Inclusion criteria	Added Inclusion criteria 12 for Part C and D only.	To expand exploration in early progressed patients within or after adjuvant therapy.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to the disease	Modified Exclusion criteria E14.	For clarification.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to the disease	Modified Exclusion criteria E17.	For clarification.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to the disease	To specify prior therapy with CDK4/6 inhibitors in exclusion criteria E23.	For clarification.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to the disease	To remove strong and moderate CYP3A inducers in exclusion criteria E24.	To correct and update.

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary, Section 1.4 PK and PD flow chart, Section 9.2.1 Sampling time and sample blood volume, Section 9.5 Sampled blood volume, Section 13.4.5 Analyses of PK and PD variables	Updated the PK sampling schedule to include the BID sampling schedule in Parts A, B, C and D and follow-up in Part B and D, and to specify that food effect assessment is not needed for BID Schedule dose in Part A.	To include BID patient and plan the PK/PD follow-up.
Tabulated clinical trial summary, Section 13.1 Determination of sample size, and Section 13.1.1 Sample size of the escalation phase for SAR439859 as monotherapy (Part A)	Updated the sample size number to include the BID extension in Part A.	To include the BID patients in Part A.
Appendix H Pharmacokinetic and pharmacodynamics flow chart for Part C and D	Removed this appendix.	For consistency with new schedule.
Appendix H Protocol Amendment History	Added an Appendix with details of past protocol amendment changes as per the new template requirements.	Added this Appendix as per the new template requirements.
Global	Minor edits and typo fixes.	To improve clarity.

Amendment [3]: [27-Jul-2018]

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Rationale for the amendment

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary and Section 8.1.1.1 SAR439859	Removed the 10 mg formulation for SAR439859.	Administrative changes/correction to SAR439859 10 mg dose strength.

Amendment [2]: [23-Jul-2018]

This amendment is not considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Rationale for the amendment

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary, Section 1.3 Flow Chart, Section 9.7.1 Criteria for response and Section 13.4.6 Analyses of antitumor activity/efficacy analyses	Added independent imaging central reading of tumor assessment to patients treated in Part B monotherapy expansion phase.	Objective response rate (ORR) is the primary efficacy objective in Part B of the study. The purpose of this amendment is to introduce the evaluation of tumor assessment using an independent central review (ICR) to reduce bias, inconsistency, variability, and to enhance credibility of assessments, whilst ensuring interpretability and in view of any potential submission to a health authority. The primary and secondary efficacy endpoints will be modified to take into account the evaluation made by the ICR.
Tabulated clinical trial summary, Section 5.2 Secondary Objectives and Section 13.4.6 Analyses of antitumor activity/efficacy analyses	Added evaluation of "Time to first tumor response (CR, PR)" as a secondary objective in Parts B and D.	Time to first tumor response (CR, PR), is added to allow efficacy comparison and alignment of SAR439859 with competitors, to see if the tumor response with study treatment is induced rapidly at first tumor evaluation or later.
Tabulated clinical trial summary, Section 5.3 Exploratory objectives and Section 9.4.4 Tumor biopsy to assess estrogen receptor degradation	Added other breast cancer biomarkers exploration as an exploratory objective.	In addition to the analysis of ER by immunohistochemistry (IHC) as described in the protocol for patients who will consent to paired biopsies, additional exploratory biomarker analyses include: • Ki67 is a widely used marker of cellular proliferation, and Progesterone receptor (PgR) expression is regulated by ER activity. IHC of Ki67 and PgR in biopsies will be performed to determine the effect of SAR439859 on the tumor. • ER-regulated gene signature. Effects of SAR439859 on expression of genes regulated by the ER can reflect biological activity of SAR439859. RNA will be extracted from the biopsies and levels of all of the RNA expressed in the tumor will be assessed (with a focus on ER regulated genes).

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary, Section 1.3 Flow chart, Section 1.4.1 Part A, Section 1.4.2 Part B, Section 5.3 Exploratory objectives, Section 7.2 Inclusion criteria, Section 9.4.4 Tumor biopsy to assess estrogen receptor degradation, Section 12.2 Baseline evaluation, Section 12.4.5 Cycle 1 Day 15 and Section 12.5.4 Cycle 2 Day 22	Modified the study plans with regards to tumor biopsy.	In order to gain a greater understanding across a larger number of patients than previously planned, and after approval of amendment 02, biopsies will be mandatory for all patients enrolling in Part A. The inclusion criterion I10 will be modified accordingly. Also, the number of patients with optional paired biopsies will be increased from 3 to at least 10 in Part B, in order to obtain more data on target engagement and biological activity of SAR439859, to explore the effect of SAR439859 on various biomarkers and potential correlation with clinical and radiological effect. The criteria I.11 will be modified accordingly. In addition, the timing of these biopsies will be modified and changes are implemented in the appropriate sections throughout the protocol. In order to ensure consistency in the assays, a central laboratory will be used for each of the biomarker analysis and either the biopsy block (preferred option) or approximately 8 x 5-µm freshly-sectioned FFPE slices on slides (for IHC analysis) and 3 x 10-µm freshly-sectioned FFPE slices (for RNA analysis, if available) will be obtained from each biopsy. Baseline biopsy will be either a fresh biopsy (preferred) or a recent/archival biopsy (within past 3 months prior to initiation of study treatment) from a tumor site, (primary tumor, local recurrence or metastatic site) in order to most accurately capture the tumor characteristics at the start of the study. The on-treatment biopsy will be performed at the end of Cycle 2 and should be from the same tumor site as the baseline biopsy.
Tabulated clinical trial summary and Section 7.2 Inclusion criteria	Modified Inclusion Criteria I05 for patients enrolled in Part B.	Regarding chemotherapy in Part B, only one prior chemotherapy line for advanced disease is allowed.
Tabulated clinical trial summary, Section 1.3 Flow chart, Section 1.4.1 Part A, Section 5.3 Exploratory objectives, Section 7.2 Inclusion criteria, Section 12.2 Baseline evaluation and Section 12.4.4 Cycle 1, between Day 1 and Day 15 (Part A only)	Added FDG PET/CT as a procedure in addition to FES PET in Part A.	FDG PET/CT is sensitive and specific for evaluating tumor response; the tumor density measurement is a good indicator and provides a reliable quantitative means of monitoring the tumor. It should be noted that a negative FES-PET does not rule out the presence of tumor, as ER-negative metastases are not visible on FES-PET. The combination of FES-PET and CT may, however, largely overcome this issue by giving insights in tumor lesions on CT that are FES negative. Similarly, the effect of upfront PET/CT with the tracers FES and FDG is anticipated to improve tumor detection. The FDG PET/CT is to be done at baseline and on-treatment. FDG PET/CT is sensitive and specific for evaluating tumor response but cannot be used in patients whose baseline FDG PET/CT results are negative for tumors.
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to the disease	Modified Exclusion Criteria E14 by adding fulvestrant washout period.	Since the ERs may remain occupied even after fulvestrant treatment is completed due to the fulvestrant's half-life of ~6 weeks, a withdrawal of fulvestrant prior to FES PET scan is necessary to prevent effects on FES uptake in Part A of the study and to allow ER receptor binding by SAR439859.

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary and Section 7.3.2 Exclusion criteria related to the disease	Modified Exclusion Criteria E16.	Clarification of prothrombin value within therapeutic range in case of treatment with anticoagulation.
Tabulated clinical trial summary and Section 8.1.1.1 SAR439859	Updated SAR439859 dose strengths.	SAR dose strengths of 1mg, 10 mg, 50 mg, and 100 mg were planned for use during the study. Even though 1 mg was produced and used during preclinical studies, it was never released and will not be used for this study.
Tabulated clinical trial summary, Section 1.3 Flow chart, Section 1.4.1 Part A, Section 1.4.2 Part B, Section 1.4.3 Parts C and D and Section 9.4.2 Estrogen receptor 1 gene mutation status in circulating free DNA	Added estrogen receptor sampling (ESR001) exploratory analysis at end of Cycle 2.	To capture the change in ESR1 tumor cfDNA level during treatment with SAR439859. Levels of tumor-derived cfDNA may reflect tumor volume and effects of SAR on the tumor. Levels of ESR1 in cfDNA will be assessed pre-treatment (at baseline) and during treatment (at the end of Cycle 2) in all parts of the study.
Tabulated clinical trial summary, Section 4.3.1 Preclinical data, Section 7.3.2 Exclusion criteria related to the disease, Section 8.6 Concomitant treatment	Updated recommendation with regards to concomitant treatment to be avoided during treatment period.	As described in Investigator brochure (section 7.2.3), available in vitro data showed that the biotransformation of SAR439859 occurs mainly through non-CYP enzymes (around 80% of hepatic clearance) involving UGT1A1 and 1A4. CYP2C8 and CYP3A are involved in SAR439859 oxidative metabolism. Therefore, drugs that are potent inhibitors of CYP3A or CYP2C8 and UGTs (atazanavir, lopinavir, ketoconazole, and quercetin) should not be administered with SAR439859, as well as drugs that are strong or moderate inducers of CYP3A. In vitro studies results showed that SAR439859 has a potential to induce CYP3A, CYP2B6, CYP2Cs and UGTs, therefore drugs which are mainly metabolized by these enzymes should be closely monitored since the efficacy of these drugs may be decreased by concomitant use of SAR439859. In addition, SAR439859 has potential in vitro to inhibit P-gp transporters. As a consequence, criteria E21, E22 and concomitant medication Section 8.6 will be modified accordingly.
Section 1.4.2 Part B and Section 1.4.3 Parts C and D, Section 8.6 Concomitant treatment, Section 9.2.1 Sampling time and sample blood volume and Section 9.5 Sampled blood volume and Appendix H	Revised PK sampling in parts B and D.	It was planned to collect samples according to a full PK sampling schedule in at least 12 subjects when SAR439859 is given alone (Part B) or in combination with Palbociclib (Part D). This sample size is deemed adequate to address PK objectives of TED14856 study and to build population PK structural model. The other patients of the expansion part are to be sampled according to a sparse sampling design in order to limit patient burden and to be able to derive individual PK parameters using the population PK model. PK parameters will be used to establish the exposure-response/safety relationship analysis. At this stage of the knowledge on PK profiles of the compound time windows for PK sample collection are defined in this amendment#2.
Section 9.2.5 PK parameters	Updated PK parameters.	CLss/F is added for SAR439859.
Section 9.5 Sampled blood volume	Updated footnote for blood sample volume in Table 19.	Footnote added to specify full and sparse samplings.
Appendix I Time window range for PK sampling	Appendix I deleted.	

Amendment [1]: [15-Jun-2017]

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Rationale for the amendment

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary and Section 7.2 Inclusion criteria	Clarified Inclusion criteria I06.	Advanced treatment setting of prior endocrine therapy is specified for patients entering all parts of the study (A, B, C, and D) in the formulation of inclusion criteria 06.
Tabulated clinical trial summary and Section 7.3 Exclusion criteria	Modified exclusion criteria E04.	Clarification of exclusion criteria 04 to reflect the actual concern related to potential inclusion of HIV positive patients and allowing such patients to be treated.
Tabulated clinical trial summary and Section 7.3 Exclusion criteria	Clarified exclusion criteria E11.	The length of time without recurrence/relapse for patients with brain metastases that have been previously totally resected or irradiated is specified.
Tabulated clinical trial summary and Section 7.3 Exclusion criteria	Clarified exclusion criteria E23.	Reformulation of exclusion criteria 23 for better clarity.
Section 6.2.2 Classical dose phase dose escalation strategy (Part A and C)	Improve clarity of Table 2 - Classical dose escalation phase.	Reformulation of the statement “or implementation or prophylactic/curative therapies” for better clarity.
Section 8.6 Concomitant treatment	Correct inconsistent duration of washout period for prior medications.	Patients taking atazanavir, lopinavir ritonavir, saquinavir (antiviral), ketoconazole, itraconazole (antifungal), and quercetin (antioxidant), strong and moderate CYP3A inducers, strong and moderate CYP3A inducers, or strong CYP3A inhibitors at the time of the screening visit should remain ineligible to enter the study until administration of the prohibited agent can be safely discontinued, and an appropriate period of time has elapsed (2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest).

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